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Working with the U.S. Food and Drug Administration to obtain approval of products under the Animal Rule

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While the development of medical products and approval by the U.S. Food and Drug Administration (FDA) is well known, the development of countermeasures against exposure to toxic levels of radiation, chemicals, and infectious agents requires special consideration, and there has been, to date, little experience in working with the FDA to obtain approval of these products. The FDA has published a regulation entitled "Approval of Biological Products when Human Efficacy Studies are not Ethical or Feasible." This regulation, known simply as the "Animal Rule," was designed to permit approval or licensing of drugs and biologics when efficacy studies in humans are not ethical or feasible. To date, 12 products have been approved under the Animal Rule. It is highly recommended that sponsors of products that are to be developed under the Animal Rule meet with the FDA and other government entities early in the development process to ensure that the efficacy and safety studies that are planned will meet the FDA's requirements for approval of the product.

Keywords: Food and Drug Administration; Animal Rule; efficacy; safety

Introduction

The development of products to prevent or treat the medical consequences of chemical, biological, or radioactive exposure has become of increasingly critical importance in recent years as terrorism has become a global threat over and above the long-existing, traditional wartime threats. While the development of medical products and approval by the U.S. Food and Drug Administration (FDA) is well known in the pharmaceutical, biotechnology, and medical device industries, the development of countermeasures against exposure to toxic levels of radiation, chemicals, and infectious agents requires special consideration, and there has been, to date, little experience in working with the FDA to obtain approval of these products.

The FDA has the regulatory authority to review and approve new products or new uses of marketed products that are meant to prevent or mitigate the effects of toxic exposures. In May 2002, the FDA published "Approval of Biological Products when Human Efficacy Studies are not Ethical or Feasible" (21 CFR 601 Subpart H for Biologics, as well as 21 CFR 314 Subpart I for New Drugs).[1,2] This rule, known simply as the "Animal Rule," was designed to permit approval or licensing of drugs and biologics that are intended to reduce or prevent serious or life-threatening conditions caused by exposure to biological, chemical, radiological, or nuclear substances when human efficacy studies are not ethical or feasible. This rule amends drug and biological product regulations to identify the information needed to provide substantial evidence of the efficacy of new drug and biological products only when human efficacy studies are not ethical and field trials are not feasible. The new rule does not address the need for safety data, which still must be established through human clinical trials. As of the time of this review, the FDA has approved 12 products under the Animal Rule (Table 1). These products include new products as well as previously approved products with new indications.

Additional challenges for product development include the practical requirements that the product be available at the scene of an incident within a short time, be able to be administered in the field

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Table 1. Products approved under the Animal Rule

Product	Indication	Date approved
Pyridostigmine bromide	Increase survival after exposure to soman nerve gas poisoning	February 5, 2003
Cyanokit® (containing the drug hydroxocobalamin, intravenous tubing, and a sterile spike for reconstituting the drug product with saline)	Known or suspected cyanide poisoning	December 15, 2006
Levaquin® (levofloxacin)	Treat plague or reduce the risk of getting plague after exposure to *Yersinia pestis*	April 27, 2012
Raxibacumab	Treat inhalational anthrax	December 14, 2012
Botulism antitoxin heptavalent (A, B, C, D, E, F, G)-(equine)	Treat patients showing signs of botulism following documented or suspected exposure to botulinum neurotoxin	March 22, 2013
Ciprofloxacin	Treatment and prophylaxis of plague due to *Yersinia pestis*	February 2, 2015
Anthrasil™, anthrax immune globulin intravenous (human)	Treat patients with inhalational anthrax in combination with appropriate antibacterial drugs	March 25, 2015
Neupogen® (filgrastim)	Treat patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome)	March 30, 2015
Avelox® (moxifloxacin)	Treat patients with plague, including pneumonic plague and septicemic plague, and for prevention of plague in adult patients	May 8, 2015
Neulasta® (pegfilgrastim)	Treat adult and pediatric patients at risk of developing myelosuppression following a radiologic/nuclear incident	November 13, 2015
BioThrax® (anthrax vaccine adsorbed)	To prevent disease following suspected or confirmed exposure to *Bacillus anthracis*	November 23, 2015
Anthim® (obiltoxaximab)	Injection to treat inhalational anthrax in combination with appropriate antibacterial drugs	March 18, 2016

with minimal medical expertise, and be stable under field storage conditions.

This review summarizes the Animal Rule and describes the procedures for working with the FDA to ensure a development program that is cost effective and generates the data needed to support approval or licensing of a drug or biologic in this arena. The Animal Rule is not an expedited path to marketing approval of a product and presents many unique challenges that traditional development programs do not face.

The Animal Rule

Approval of any new drug or biologic requires submission of data to the FDA that provides substantial evidence of efficacy in the target indication. The Animal Rule states that the FDA will rely on evidence from only animal studies to provide substantial evidence of effectiveness when all of the following criteria are met: (1) there is a reasonably well-understood pathophysiological mechanism of the toxicity of the toxic substance and its prevention or substantial reduction by the product; (2) the effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans; (3) the animal study end point is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and (4) the data or information on the kinetics and

pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

The choice of an animal model that predicts the response in humans following exposure is of critical importance to the application of the Animal Rule.[3,4] The Animal Rule allows approval based on a single animal species, if the animal model is sufficiently well characterized; however, the usual expectation is that efficacy will be demonstrated in more than one species. In order to support approval based on one animal species, in general more than one efficacy study using that species would need to be conducted to demonstrate reproducibility of the results. Alternatively, a combination of an animal model and human clinical studies in a medical condition that is similar in pathophysiology may be sufficient to demonstrate efficacy. For example, a countermeasure to a vesicant agent causing corneal erosions could be studied in a combination of a rabbit ocular injury model and in patients with corneal erosions. Such a combination of studies would show activity in healing erosions in patients and healing erosions in the animal model caused by the toxic agent. Furthermore, the patient study would support the safety of the product.

The FDA has published a guidance document on the development of animal models that can be used to demonstrate efficacy under the Animal Rule.[3] This guidance outlines the principles to be considered in development of the animal model. These considerations include characteristics of the challenge agent used to simulate the exposure in the animal. Ideally, the challenge agent should be the same as the etiologic agent causing the human disease, or include a demonstration that the substitute produces the same pathophysiology in the animal.

The animal model should show the same pathogenic characteristics of the disease in humans and should include factors such as sex, age, and immune status. Demonstration of this similarity may require extensive natural history and clinical and histopathologic study to compare the animal to human disease. Also, the route of exposure to the toxic agent may influence the characteristics of the disease in humans and may be a factor in how the animal is exposed and the route of administration of the countermeasure. Of course, the dose of the challenge agent should be well characterized and reproducible, and the dose in the animal should be understood in relation to the dose in humans that produces the toxic effects.

As appropriate, the pharmacology of the countermeasure should be well understood in both the animal model and in humans. Any of the standard nonclinical and clinical studies to evaluate toxicity in animals, safety in humans, pharmacokinetics, and pharmacokinetic drug interactions or synergism/antagonism with products likely to be used in combination should be evaluated as part of the development program. The timing of administration when the countermeasure will be effective needs to be demonstrated to determine the optimal time to treat and when treatment is too late to be effective.

The selection of the dose to be used in humans can be a challenge under the Animal Rule when efficacy cannot be established in clinical studies. In such a case, the dosing regimen should be based on sufficient pharmacokinetic and pharmacodynamic data and extrapolation of exposure information from animals and healthy human data. If the therapeutic agent has the potential to cause undesired effects in healthy humans, microdose studies for pharmacokinetics could be considered if a sensitive bioanalytical assay is available.

The essential data elements and the basis for a complete development program to be considered and gathered from the animal studies include the following.

- Characteristics of the agent that influence the disease or condition
  - The challenge agent
  - Pathogenic determinants
  - Route of exposure
  - Quantification of exposure
- Host susceptibility and response to etiologic agent
- Natural history of the disease or condition: pathophysiologic comparability between animal model and human
  - Time to onset of condition
  - Time of progression of disease or condition
  - Signs and symptoms
- Trigger for intervention
- Characterization of the medical intervention
  - Intervention product class
  - Mechanism of action
  - *In vitro* activity

- Activity in similar disease or condition
- Pharmacokinetics in unaffected animals/humans
- Pharmacokinetics/pharmacodynamics in affected animals/humans
- Pharmacokinetic interactions with products likely to be used concurrently
- Synergy or antagonism with products likely to be used concurrently

The design of the animal studies to demonstrate efficacy must be as robust as efficacy studies in humans, with the studies conducted under good laboratory practice, to the extent practicable, and Animal Care standards, under a protocol with predefined end points that are relevant to the human disease. The route and administration and dosing must be relevant to the human disease.

Combination products require particular attention and may require additional studies.[5] The combination may be two or more drugs that are intended to be administered together or a combination of a drug or biologic and a medical device. Combination products have been discussed in guidance documents from the FDA, but for products developed under the Animal Rule, the Review Division, and possibly the Center for Devices and Radiological Health, should be consulted.

Finally, human safety data are required to support the approval of the product. Safety data can be evaluated in healthy volunteers or, if there is a significant risk associated with the product, in studies in patients with a similar disease if a population can be identified and justified on a risk–benefit balance. The size of the clinical safety database depends on many factors, including duration of exposure and seriousness of the disease. Existing safety data for the product administered by the same route of administration would generally be satisfactory for products that are already marketed for another indication and known to have an acceptable safety profile in the populations that would receive the product for the new indication. However, differences in dose and duration of exposure may influence the amount of safety data required. A longer exposure under the new indication may require additional safety information if, for example, the original approval of the product was for acute administration and the new indication required chronic administration. A product used for prophylaxis may require more safety data, as there would be subjects treated without the risk of developing the human disease. A new product without a marketing history may require substantial safety data, as expected for a new chemical entity or biologic.

Approval of a product under the Animal Rule will generally be subject to three requirements.

Postmarketing studies

Postmarketing studies, such as field studies, will be required to verify and describe the product's clinical benefit and to assess its safety when used as indicated when such studies are ethical and feasible. The marketing application must include the plan for such studies to be done postapproval.

Approval with restrictions to assure safe use

If there is a determination that the product can be used safely only under the approved labeling, restrictions on distribution or access may be imposed. Once a product is approved, the product could be used off label for any indication, and restricted distribution may be required if deemed not safe for such use.

Information to be provided to patient recipients

Information regarding the conditions of approval, such as efficacy based only on animal studies, as well as directions for use (dose and route of administration), contraindications, foreseeable risks, adverse reactions, and drug interactions, must be provided to the patient recipient before administration or dispensing, if possible.

A useful product development tool is the Target Product Profile (TPP).[6] The purpose of a TPP is to provide a format for discussions between a sponsor and the FDA that can be used through all phases of drug development, including postapproval. The TPP embodies the notion of beginning with the goal in mind.

Meeting with the FDA

There are many challenges and considerations that may not be readily apparent to the developer of the product. It should be noted that the FDA anticipates that the nonclinical and clinical safety development programs will proceed in a manner similar to that of drugs developed under traditional regulatory pathways, and development of these products should not be considered an expedited pathway to approval. In fact, the development process may be

much more challenging than a traditional development program. Therefore, the FDA encourages developers/sponsors of countermeasures to meet early with the FDA to obtain agreement on the development program. The sponsor should also have early discussions with public health officials and military officials regarding the potential need for, and operational use of, the investigational drug, and discuss their input with the FDA. The FDA Counter-Terrorism and Emergency Coordination Staff (CTECS) can also be a valuable resource before meeting with disease experts in an FDA Review Division.[7] CTECS meetings are not formal meetings, and any discussion is advisory and not binding, but it provides a unique perspective on how to approach the discussion with the review division. CTECS provides presentations at public meetings to facilitate drug development on medical countermeasures against the effects of chemical, biological, radiological, and nuclear agents. Sponsors of such medical countermeasures are often small companies, academicians, or other federal agencies with limited drug development experience who need assistance in navigating the complexities of the FDA. A regulatory consultant can provide invaluable support and guidance in this context—a naive product developer should take advantage of such consultants to avoid wasteful and nonproductive activities.

Before meeting with the FDA, the product developer should have a development plan in place that includes the following elements:

- The proposed indication and whether a drug can be developed under the Animal Rule
- The design of an animal study as it relates to the anticipated clinical use of the drug during an incident
- The development and/or selection of the animal models, including, when necessary, the design of the natural history studies
- The results of the proof-of-concept studies
- A plan for manufacturing the drug substance and drug product
- The proposed methods for selecting an effective dose and regimen in humans
- The design of the adequate and well-controlled animal efficacy studies intended to provide the primary evidence of effectiveness of the drug
- The proposed approach for ensuring the quality and integrity of data
- The size and composition of the human safety database
- Plans or approaches for conducting the required postmarketing studies (e.g., field studies) to demonstrate safety and clinical benefit when such studies are feasible and ethical
- Timelines and/or milestones for FDA feedback or meetings
- Eligibility for expedited development and review designation programs
- Additional issues critical to the sponsor's funding agencies

Target Product Profile

A useful product development tool is the Target Product Profile (TPP).[6] The purpose of a TPP is to provide a format for discussions between a sponsor and the FDA that can be used through all phases of drug development, including postapproval. The TPP embodies the notion of beginning with the goal in mind.

The procedure for meeting with an FDA Review Division is defined in guidance documents.[7] Generally, the procedure is to file a meeting request with the new drug or biologic review division, including background information, a summary of the proposed development program, and a draft list of specific questions for which to obtain FDA advice. The appropriate review division to contact corresponds with the indication of the product. The meeting request can specify whether a face-to-face meeting is desired or whether a teleconference or written response is desired. The complexity of issues generally warrants a face-to face-meeting. The FDA will respond to the request within 2–3 weeks with a meeting date. A full briefing document with detailed background materials, final detailed questions, development plans, and efficacy study outlines will be required to be submitted at least 30 days before the meeting.

The questions to be asked of the FDA are critical to a successful interaction. Naive or open-ended questions asking the FDA what the sponsor should do are not helpful and will usually result in a list of guidance documents for the sponsor to read. The questions should be based on a proposed development plan with as much detail as can be known at

the time of the meeting and should be questions that the FDA can answer with a "yes" or "no" response. When the FDA answers "no" to a question, it is almost always followed by their advice on why the sponsor's proposal does not meet FDA requirements and what can be done to meet the requirements.

A few days before the meeting, the FDA usually provides draft responses to the meeting questions so that the sponsor has adequate time to prepare for the discussion with the FDA at the meeting. Meeting attendees should understand that they have a limited opportunity to hold discussions with the FDA and should make efficient use of the 1-h time limit for the meeting. Therefore, there should be no presentation of information that was already included in the briefing document. If the briefing document was not sufficient to clearly inform the FDA and has resulted in confusion on the part of the FDA with regard to the development plans, it is often recommended to limit any presentation to those points. The discussion during the meeting should focus on those areas where the sponsor does not understand FDA advice or where the sponsor wants to discuss other alternatives to meeting FDA requirements. During the meeting, the FDA will finalize the preliminary responses, capturing any meeting discussion, and will provide final minutes of the meeting within 30 days after the meeting.

Special Protocol Assessment

It is recommended that the proposed animal efficacy studies be submitted for a Special Protocol Assessment (SPA) procedure after meeting with the FDA to discuss the general plan, animal model, dosing, end points, and other matters. By regulation, the FDA has 45 days to review and comment on an SPA, and the sponsor will receive a formal Agreement or No Agreement letter. If the sponsor receives a No Agreement letter, they have an opportunity to resubmit the protocol after appropriate changes have been made or to request an urgent meeting to discuss and resolve any disagreements on the FDA's advice. Such a meeting (called a type A meeting) can be scheduled within 30 days of a request. Once agreement is reached on the design of the animal efficacy studies, the FDA is committed to accept the data from such a study as long as the study is conducted according to the agreement and no change in the scientific understanding of the disease or product has occurred in the meantime.

Expedited development and review opportunities

The FDA has several programs available that can be accessed to expedite the development and review of medical products for the treatment of serious diseases where these is an unmet medical need.

- *Fast track*: Application requires nonclinical data to demonstrate the potential to address an unmet medical need. Benefits are actions to expedite development and review and eligibility to submit the marketing application under rolling review.
- *Priority review*: Six-month review clock compared to the normal 10-month review clock.
- Note that the Breakthrough Therapy designation is not available for products being developed under the Animal Rule, since clinical data are required.

Conclusions

The Animal Rule has provided a mechanism for the development of products intended to reduce or prevent serious or life-threatening conditions caused by exposure to biological, chemical, radiological, or nuclear substances when human efficacy studies are not ethical or feasible. Sponsors of such products should understand that the FDA is their best source of advice on how to develop the product and should consider them to be their development partners.

Conflicts of interest

The authors declare no conflicts of interest.

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