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FDA perspective on antivirals against biothreats: Communicate early and often☆

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Abstract

Development of antiviral products for certain highly pathogenic viruses with limited available treatments, such as viruses that may have biothreat potential, is critically important and challenging. The mission of the FDA is to protect the public health by assuring the safety, efficacy and quality of such products. Human clinical trials are critically important whenever relevant naturally occurring diseases can appropriately be studied. In selected situations when clinical studies are not ethical and field efficacy studies are not feasible, the Animal Rule (67 FR 37988, 2002) introduces the possibility of drug/biologic approval/licensure based on efficacy studies in animals, and appropriate human safety and pharmacokinetic information. This approach necessitates the development of well-delineated animal models predictive of human disease and treatment responses, and plans for adding human information if suitable circumstances arise. Efficient development of therapeutics against these agents requires collaborative efforts among industry, academia and federal agencies.
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1. Background

The Food, Drug, and Cosmetic Act of 1938 mandated that drugs be labeled for safe use. In 1962, the Kefauver-Harris Amendments added efficacy requirements. The mission of the Food and Drug Administration (FDA) includes assuring safety, efficacy and quality of drugs and biological products, which undergo premarketing review for both safety and efficacy. The Agency has a number of provisions for facilitating development of products directed at serious and life-threatening diseases in areas of need. For example, accelerated approval (21 CFR 314.500-560 for drugs; 601.40-46 for biologics) allows approval based on surrogate endpoints reasonably likely to predict clinical benefit with further post-marketing evaluations to confirm benefit. Continued assessment of safety is an important element of post-marketing evaluations.

Researchers and sponsors involved with the development of therapies for infections with highly pathogenic viruses will benefit from understanding many aspects of drug and biologic regulations including the unique requirements for development under the "Animal Rule". The focus of this article is the development of antivirals for certain highly pathogenic viruses that may be considered as potential biothreat agents, such as virulent outbreak strains of filoviruses; typically these cause acute rather than subacute or chronic disease, may be imminently life-threatening, and have few or no available treatments. In addition, challenges exist when working with these viruses including laboratory facility restrictions for biosafety level three or four, site limitations, and limitations in available data about animal model feasibility. Viruses with the above-listed attributes differ from other types of highly pathogenic viruses in many aspects of their epidemiology and clinical course. Early communication with FDA including the submission of study protocols, proposals, and questions for review and feedback will promote improved utilization of resources and help to ensure that studies done to support drug development are appropriately designed and conducted, and that adequate efforts are made to avoid undue risks and resource wastage. Frequent submission of study results,

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including raw data, provide a basis for FDA development advice on an incremental basis; from a preparedness perspective, FDA may then have information available prior to a public health emergency which may warrant rapid review of the utility of investigational products to respond to the event.

2. Considerations in evaluating potential human studies

Usually drug[1] approval is based on studies involving patients with the disease for which the product is to be indicated, providing a foundation for assessment of risk-benefit balance and adequacy of instructions for use. Among the aspects of the disease that may affect study proposals is an understanding of its epidemiology including an understanding of naturally occurring epidemics with special attention to timing and location of potential outbreaks, as well as its clinical characteristics and pathophysiology. If there is potential for a virus to be used as a bioterror agent, both the mode of initial dissemination and the potential for subsequent person-to-person transmission may be important, and the possibility of differences in epidemiology and pathogenesis compared to natural disease might be raised in discussion of study proposals.

Studies of patients infected with highly pathogenic viruses may be difficult to conduct if there are limited incidence of the disease and/or sites with limited access and resources. With other rare diseases for which treatments have been studied, including examples such as unusual malignancies and poisoning events, even small amounts of clinical data have contributed to understanding the potential value of the investigational product. The product's spectrum of activity has also affected study designs, as products with activity against multiple pathogens have sometimes been studied concurrently in a variety of conditions. Sometimes it is possible to supplement the available information on the use of the investigational product with data obtained in clinical trials in related naturally occurring diseases. If disease is sporadic, it may be possible to develop protocols in advance to be ready for implementation or rapid adaptation in the event of an outbreak. With such approaches, developers have the potential to benefit populations naturally affected by the diseases, as well as potential future biothreat victims. In addition to gathering efficacy data, it is imperative that adequate safety information be generated. Initial human safety information is most often derived from drug administration to healthy volunteers if this can be done without undue risk. Safety assessment for rare indications has also sometimes taken into account experience with the use of the same product for other more common diseases.

3. Efficacy data obtained under the Animal Rule

The Final Rule for the "Animal Rule" (Food and Drug Administration, HHS, 2002) was published on 31 May, 2002 (21 CFR 314.600-650 for drugs; 601.90-96 for biologics). This rule applies only "when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible." FDA will rely on evidence from studies in animals to provide substantial evidence of effectiveness only when:

(a) "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;
(b) 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 (meaning the model has been adequately evaluated for its responsiveness) for predicting the response in humans;
(c) the animal study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity; and
(d) the data or information on pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well understood to allow selection of an effective 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."

For further information, see: http://www.fda.gov/OHRMS/DOCKETS/98fr/053102a.pdf.

4. Product development using the Animal Rule

It is important to understand that use of the "Animal Rule" is not a simplified or an expedited route to developing medical products, compared to traditional product development, and that it cannot be used in all situations. For example, the "Animal Rule" does not apply if a product can be approved using other means, such as accelerated approval. Even if criteria for its use are met, development challenges may be considerable. If a sponsor proposes to pursue "Animal Rule" development, discussions with the Agency and feedback regarding applicability of the rule may be affected by numerous aspects of the disease and the existing science base: for example, extent and nature of natural history studies in both humans and animals, extent to which animal models mirror the disease found in humans and provide the ability to correlate animal and human pharmacokinetics, and quantity and quality of information provided to support the animal models as reliable indicators of efficacy in humans. Information available for some of these issues may differ between antivirals and vaccines thus requiring a case-by-case discussion. Even where the Animal Rule is not used, animal data have sometimes provided important ancillary information to support interpretation of sparse human data, so the opportunity for sponsors to discuss animal study proposals and data with the Agency is not limited solely to pursuing

[1] The Center for Drug Evaluation and Research (CDER) is responsible for the review of drug and therapeutic biologic applications. The use of the word "drugs" in this paper will henceforth refer to both drugs and therapeutic biologics (e.g., monoclonal antibodies and small protein molecules). Information about vaccines and other biologics, such as antisera and blood products, should be obtained from the Center for Biologic Evaluation and Research (CBER).

approval under the Animal Rule. The Agency may take into account other information in assessing sufficiency of animal data.

5. Other data needed to develop drugs under the Animal Rule

The Animal Rule itself does not address safety evaluation, which can be planned according to general principles of drug development. It also does not address a range of issues in areas such as chemistry, manufacturing, and controls. Sponsor discussions with the Agency early in development can help to delineate the approach to each component of the Animal Rule and other more general aspects of drug development, and to establish a foundation for further incremental discussions and advice as more information about the product becomes available.

6. Drugs with approved indications

Drug development can be based on a new indication for an old drug, or development of a novel molecule or a new compound in a known class. The advantage of using a previously approved drug for a new indication may include information on efficacious dosing regimens in humans for approved indications as well as access to safety information from clinical trials and post-marketing use.

While there are advantages to studying a previously marketed drug for a new indication, there may be major gaps in data to address. For the new indication, the drug dose or duration may be different potentially requiring a significant amount of new safety data. The risk/benefit analysis may be different for diseases due to highly pathogenic viruses compared to other indications, and may vary depending on the indication sought even for the same pathogen. For example, a drug with significant safety concerns may not be appropriate for post-exposure prophylaxis of large numbers of people who may not be incubating disease, but may be considered appropriate for treatment in symptomatic patients with known high mortality from the disease.

7. Drugs not previously approved

Drugs developed against highly pathogenic viruses may represent new classes with no clinical experience. Evaluation of new drugs warrants careful consideration of the potential for conducting human clinical trials as detailed above. Where there is no prior information on safety or efficacy in humans, more nonclinical as well as human clinical and safety information would be required for approval/licensure. When possible, varying amounts of human efficacy and safety information may be obtained studying the product for a different indication (e.g., other viral diseases). As discussed above, risk/benefit assessment may differ for treatment compared to prophylaxis. If products are approved using the "Animal Rule", protocols must be developed to obtain safety and efficacy data in the event of human use during an outbreak.

8. Development schedule

As products are developed for new indications using limited resources, it is critical that sponsors/developers establish early communications with the FDA. Pre-IND consultation is strongly recommended for review and feedback on preliminary data and development plans. FDA interactions are not limited to industry; academia, government or industry sponsors can initiate interactions with the Agency, whether or not they are the primary manufacturer of the proposed product. As more drugs are being developed for counter-terrorism indications, early product development may be undertaken by government entities or academia, and it is important that those entities initiate early communication with the FDA to guide effective and efficient product development. Data and protocol review are the responsibility of the Review Divisions in the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the FDA. The Office of Counter-Terrorism and Emergency Coordination in CDER is a consultative office that works with the Review Divisions and Health and Human Services (HHS) offices to promote consistent recommendations for the development of new drugs. The Office of Counter-Terrorism and Emergency Coordination is available to help new sponsors navigate very early interactions (i.e., prior to pre-IND consultation). For antiviral drugs and therapeutic biologics, the Division of Antiviral Products (DAVP) is the review division where prospective sponsors are encouraged to provide information and questions for review and feedback even at early stages of their development plans. This may lead to several incremental pre-IND interactions depending on characteristics of the product and product development. General information about the DAVP pre-IND program is available on the FDA website at http://www.fda.gov/cder/ode4/preind/default.htm; there is substantial flexibility in pre-IND content, and sponsors have been able to initiate pre-IND interactions even if they have only limited information to submit or have development issues to discuss before deciding on a molecule for development.

The FDA evaluates proposals for and data from nonclinical and clinical studies. Initial preliminary nonclinical studies provide the framework for the continued study of the product. Early in development, it will be appropriate to assess the potential for human clinical studies. If there are questions about the feasibility or the ethics of conducting clinical trials, it is important to discuss these questions and any proposals for using the "Animal Rule" with the Agency. If a sponsor wishes to pursue studies under the "Animal Rule", protocols for the animal studies should be submitted to the FDA, including detailed information about the natural history of the disease in animal models proposed for use and the rationale for using particular models. Submission of animal study protocols for review and prospective discussion with the Agency are critical as these studies may need to use limited biosafety level three or four laboratory facilities and precious supplies of animals, particularly non-human primates. Pivotal animal efficacy studies need to be performed under Good Laboratory Practice (GLP) conditions with final or near-final drug products.

The indication to be studied will drive the design of the animal efficacy protocols. Study designs and endpoints may differ for pre-exposure prophylaxis, post-exposure prophylaxis, or treatment. The drug formulation may also influence the indication to be sought. For example, an I.V. formulation may not be practical for post-exposure prophylaxis for large populations, while an oral formulation may not be appropriate for seriously ill patients. To promote efficacious and efficient use of limited resources while minimizing risk to humans from accidental exposure to virulent pathogens, the discussion of animal protocols should include the determination of appropriate endpoints, evaluation of evidence for whether the animal models are predictive of the response in humans, determination of the appropriate range of doses to bridge pharmacokinetic information in animals and humans, and the demonstration of adequate exploration of treatment timing and duration relative to clinically evident manifestations of illness in both the animal and the human.

Nonclinical aspects of development plans typically may involve preliminary studies completed in small animals and submitted for discussion before proposing pivotal studies in non-human primates or other appropriate large animal species if Animal Rule development is agreed upon. Pivotal studies should use GLP and should be conducted with final scalable manufactured product developed using Good Manufacturing Practices (GMP). FDA Guidance on GLP and GMP can be found at http://www.fda.gov/ora/compliance_ref/bimo/glp/default.htm and http://www.fda.gov/cder/guidance/index.htm#CGMPS-Eff, respectively. Additional protocols to be discussed with the Agency include interaction studies to evaluate possible interference with other therapeutics including vaccines. The toxicology studies to be performed prior to initial human dosing and associated with the more advanced stages of product development can be discussed with the Agency in pre-IND interactions and are addressed in guidance on the FDA website (see http://www.fda.gov/cder/guidance/index.htm#Pharmacology/Toxicology).

Studies administering the investigational product to humans are governed by Investigational New Drug (IND) regulations. Data necessary for submission of an IND are addressed in guidance on the FDA website (see http://www.fda.gov/cder/guidance/phase1.pdf and other relevant documents at http://www.fda.gov/cder/guidance/index.htm) and can be discussed with the Agency during pre-IND interactions. Discussions of potential animal efficacy studies initiated at the pre-IND stage can be continued as appropriate with submissions to the IND after human studies are initiated. Protocols for the human pharmacokinetic and safety studies in appropriate populations should be submitted to the FDA for review to ensure that the appropriate clinical and laboratory parameters are to be monitored. Depending on the results of the pharmacokinetic studies, there is the potential need for additional dose-escalation studies. Additional safety studies may be required if dose escalation is needed. Multiple-dose studies may be required. The Agency has been developing evaluation plans for studying certain adverse events, including drug effects on the QT interval. For guidance in these areas please check the FDA website at http://www.fda.gov/cder/guidance/index.htm for general information about guidance documents and http://www.fda.gov/cder/guidance/6922fnl.htm for specific information on QT studies.

Any products approved/licensed for use under the "Animal Rule" are required to state in the labeling that approval is based on animal data, and there may be restrictions on distribution of the product. An important caveat of the "Animal Rule" is that safety and efficacy information on the marketed product is to be obtained in the event of a disease outbreak. Protocols to capture this information must be developed and discussed with the Agency.

9. Conclusion

This is an exciting time in the development of countermeasures for biologic threat agents including highly pathogenic viruses. Efficient development requires the cooperation of industry, academia and government agencies to establish acceptable animal models and to streamline study development for best resource use. This approach mandates collaboration and early and frequent communication with the FDA. Early submission of study protocols and trial results is necessary to promote expeditious product development. Decisions can then be made about the best regulatory approach to approval/licensure. Maximal effort to submit protocols for FDA review and to communicate with the Agency, prior to conducting the trials, can help to avoid inadequate trials from a design, endpoint and/or monitoring perspective, that could necessitate additional studies that would waste precious time and resources. It is, therefore, critical that drug developers contact the Agency early and often.

Reference

Food and Drug Administration, HHS. New Drug and Biological Drug Products: Evidence needed to demonstrate effectiveness of new drugs when human efficacy studies are not ethical and feasible. Federal Register 2002 May 31; 67(105), 37988–37998.