Assessing a drug for an eradicated human disease: US Food and Drug Administration review of tecovirimat for the treatment of smallpox

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The development and ultimate approval of tecovirimat for the antiviral treatment of smallpox, a disease that has been eradicated from the world for nearly 40 years, required a unique regulatory approach based on the US Food and Drug Administration's Animal Rule. We summarise the regulatory pathway and describe the challenges involved.

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Introduction

Smallpox is a serious and life-threatening disease caused by infection with variola virus, which is in the Orthopoxvirus genus of viruses. Historical mortality in variola major, the more common and serious form of smallpox, has been commonly cited as 30%.[1] Following an intense global smallpox vaccination campaign, worldwide eradication was declared in 1980. Despite its eradication, smallpox remains a possible threat to national security and public health due to the biothreat potential of variola virus.[2] As routine smallpox vaccination in the USA ended in the 1970s, most of the US population is susceptible to smallpox. Therefore, effective medical countermeasures, including antiviral therapies, will be crucial in the event of a smallpox outbreak. Tecovirimat, an orally bioavailable antiviral drug, was developed by SIGA Technologies (Corvallis, OR, USA) for the treatment of human smallpox.[3] On July 13, 2018, the US Food and Drug Administration (FDA) approved tecovirimat to treat human smallpox disease caused by variola virus.[4] Tecovirimat is the first antiviral drug approved for this indication.

Background

Smallpox drug development presents substantial challenges. Because smallpox is a potentially serious and life-threatening disease, but one that does not occur naturally, clinical efficacy trials are not feasible, and challenge studies with variola virus in humans would never be permitted. To address circumstances where it is not feasible nor ethical to do efficacy trials in humans, in 2002, the FDA established the Animal Rule (Code of Federal Regulations title 21, part 314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval.[5–7] Drug development using the Animal Rule is extremely challenging, and early communication and close collaboration between drug developers and the FDA is essential. Furthermore, input and support from other stakeholders (governmental and non-governmental) might be vital in facilitating drug development.

Although the Animal Rule provides a statutory foundation for drug approval when human efficacy trials are not possible, applying this regulatory approach to smallpox drug development is especially challenging. In theory, the ideal animal model for smallpox would involve animals infected with variola virus, but natural variola virus infection and smallpox disease are specific to humans—a characteristic that enabled eradication of the disease. Animal models using variola virus, including non-human primate (NHP) models, are not consistently reproducible, require unnaturally high viral challenge doses, and do not mimic human smallpox disease.[8,9] Furthermore, studies of variola virus present numerous feasibility challenges due to worldwide restriction of variola virus research to two maximum-containment laboratories—one in the USA and one in Russia.

Given the unique complexities and challenges of smallpox drug development, the FDA organised a workshop in 2009 and an Advisory Committee meeting in 2011 to elicit external input.[8,9] When considering animal models that could be used for drug development, evidence from studies, as well as the perspectives from the 2011 Advisory Committee, experts in the field, and other external stakeholders were taken into consideration. The FDA concluded that both the scientific and practical limitations of variola virus NHP models available at the time made them unsuitable for use in pivotal animal efficacy studies to support the regulatory approval of smallpox therapeutics, and that an alternative development pathway should be considered.[9] Although whether an adequate variola virus animal model could ever be developed to support regulatory approval was uncertain, other animal models of lethal, non-variola orthopoxvirus infection had been developed, including monkeypox virus infection of NHPs and rabbitpox virus infection of rabbits. Neither of these animal models mimics all aspects of human smallpox; however, they are lethal models, and animals do develop certain characteristic disease signs that are shared with human smallpox, such as fever and skin lesions. Furthermore, compared with the variola NHP model, disease manifestations in these non-variola models tend to be more consistent and predictable, and the models are more practical for generating pivotal efficacy and pharmacokinetic data in infected animals to support approval under the Animal Rule.[9]

Based on these considerations, the 2011 Advisory Committee and the FDA agreed that data from a

combination of lethal animal models using surrogate orthopoxviruses could be used as evidence along with, or potentially in place of, animal studies using variola virus.[9] Given that no single orthopoxvirus (variola or non-variola) animal model is clinically established to be predictive of human response to smallpox treatment, demonstration of consistent efficacy in multiple different orthopoxvirus animal models was recommended to decrease the uncertainties of this approach.[9] Demonstration of efficacy was feasible for the evaluation of tecovirimat because the drug target is conserved across orthopoxviruses. To help satisfy the FDA Animal Rule requirements, detailed natural history studies with the non-variola orthopoxvirus animal models were done before the pivotal efficacy studies.[3] These natural history studies helped to establish that disease was reproducible, disease signs were relevant to human smallpox, and the design and results of pivotal efficacy studies would be reasonably expected to predict efficacy in variola virus infected humans.

Animal Rule criteria applied to the development and regulatory review of tecovirimat

For drug approval under the Animal Rule, several key requirements must be adequately addressed.[5–7] The table and the following text summarise the key criteria and describe how they were addressed for tecovirimat.

Pathophysiological mechanism of smallpox and mechanistic basis of tecovirimat

In the situation under discussion, the toxic substance is variola virus and the toxic event of concern is the illness likely to develop if humans were exposed to variola virus (either without timely vaccination or with illness developing despite vaccination). Because smallpox was eradicated nearly four decades ago, the pathophysiology of the disease in humans is not fully understood, making it difficult to know which elements of variola virus infection and pathogenesis in humans are most important to recapitulate in an animal model. However, the major clinical features of smallpox disease in humans have been well established. Tecovirimat also has a well established mechanism of action. The drug inhibits viral spread to uninfected cells by directly and specifically targeting an orthopoxvirus protein termed F13 (also referred to as VP37 or p37), which is involved in producing extracellular enveloped virions.[10,11] The viral F13 target is highly conserved in all members of the Orthopoxvirus genus, providing scientific basis for using surrogate orthopoxviruses to evaluate tecovirimat efficacy. In-vitro cell culture studies have shown broad antiviral activity and similar potency of tecovirimat against diverse orthopoxviruses, including monkeypox virus, rabbitpox virus, vaccinia virus, and most importantly, variola virus.[10] Consistent with its targeting of an orthopoxvirus-specific protein, tecovirimat had low cytotoxicity and a wide therapeutic index in inhibiting orthopoxviruses in cell culture, and no measurable activity was observed against a diverse panel of other DNA and RNA viruses.[10]

Tecovirimat efficacy in two lethal orthopoxvirus animal models using survival as the primary efficacy endpoint

Pivotal efficacy studies of tecovirimat used two well characterised, lethal animal models of non-variola surrogate orthopoxviruses: NHPs infected with monkeypox virus and rabbits infected with rabbitpox virus.[3,4,12] The timing of tecovirimat dosing was intended to assess efficacy when treatment is initiated after animals developed clinical signs of disease that are considered to be relevant triggers for the treatment of human smallpox—specifically dermal pox lesions in NHPs, and fever in rabbits. These disease signs are first observed within 3–4 days following viral challenge in these models, and resemble features of smallpox disease observed in humans following an asymptomatic incubation period.[1] The primary efficacy endpoint for these studies was survival. In both animal

	Approach and findings with tecovirimat
There is a reasonably well understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product	The pathophysiology of smallpox is not fully understood but clinical features of smallpox and the mechanistic basis of tecovirimat antiviral activity are well established
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 characterised animal model for predicting response in humans	No single animal model mimics human smallpox disease, and scientific and feasibility limitations preclude use of a variola virus animal models to establish efficacy; efficacy demonstrated using two lethal non-variola surrogate orthopoxvirus animal models: monkeypox virus infection of non-human primates, and rabbitpox virus infection of rabbits
The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity	Survival from lethal viral challenge was the primary efficacy endpoint
Availability of data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans that would allow selection of an effective dose in humans	Analyses of pharmacokinetics and pharmacodynamics data from animal models and healthy human volunteers enabled prediction of an effective dose in humans
Clinical safety to be established for the new drug product	Proposed dosing regimen (600 mg twice a day for 14 days) demonstrated to be safe and well tolerated in healthy volunteers

Table: **US Food and Drug Administration's Animal Rule criteria applied in the development and regulatory review of tecovirimat**

models, treatment with tecovirimat for 14 days resulted in statistically significant improvement in survival relative to placebo.[3,4,12]

Selection of an effective dose in humans

To select an effective dose of tecovirimat in humans for the treatment of smallpox infection, tecovirimat exposures achieved in healthy human subjects were compared with those observed in animal models of orthopoxvirus infection at the doses associated with maximum effectiveness.[3,12] To help address uncertainties inherent in this approach, the dose selected for humans should exceed the effective dose in animals, ideally by several times. For tecovirimat, the selection of a maximum human dose was constrained by neurological findings, including seizures, in animal toxicology studies.[3,12] Despite this, tecovirimat exposures achieved in healthy humans at the recommended dose are substantially higher than the therapeutic exposures in the relevant animal models.[3,12]

Tecovirimat safety in humans

Drug development under the Animal Rule requires that safety be established. The size and composition of the human safety database necessary to support drug approval depend on issues such as the proposed indication, the drug's toxicity profile, and the extent of the FDA's experience with a particular drug class. For a drug intended to treat a life-threatening disease, greater known risks or greater uncertainty about undefined risks might be more acceptable than for other drugs since the drug is expected to offer a clear benefit to patients. Outside of a public health emergency, the safety evaluation of drugs developed solely for the treatment of smallpox depends primarily on data from trials in healthy volunteers. The safety of tecovirimat was evaluated in 359 healthy human volunteers.[3,12] Most adverse events were mild, and rates were similar across tecovirimat and placebo groups. No deaths or serious adverse events were assessed as related to tecovirimat.[3,12] Importantly, as it relates to the animal toxicology findings, no seizure events were reported in human volunteers, although one asymptomatic subject discontinued tecovirimat due to an abnormal electroencephalogram, the clinical significance of which is unknown.[3,12] The safety database for tecovirimat, although small, was adequate to provide evidence of the drug's safety for the proposed indication.

Other potential uses for tecovirimat

Given the broad anti-orthopoxvirus activity of tecovirimat, the FDA recognises the interest in potentially using tecovirimat to treat other human orthopoxvirus infections—particularly monkeypox virus infection—and maintains a mechanism to provide tecovirimat for the treatment of non-variola orthopoxvirus infections should the need arise.

As outlined during the Advisory Committee discussions on May 1, 2018, the Animal Rule applies to products for which field trials to study the product's effectiveness are not feasible.[7,12] Although there are challenges involved in the study of naturally occurring monkeypox virus infection, doing such a clinical trial remains a possibility due to improving infrastructure and ongoing interest of public health experts and other stakeholders in generating these important clinical data.[12] The FDA continues to encourage the clinical evaluation of tecovirimat for the treatment of monkeypox or other orthopoxvirus diseases when feasible.

Conclusions

Based on safety and efficacy data, the FDA concluded that the overall risk–benefit profile of tecovirimat is favourable for the treatment of human smallpox disease, and that the requirements for approval under the Animal Rule have been met.[4,12] Multiple milestones in drug development and regulation were achieved with this approval. Not only is tecovirimat the first antiviral drug approved for smallpox, it is also the first drug approved to treat a disease that no longer exists in the human population. To reach these milestones, the FDA worked collaboratively with the sponsor, the research community, and other government agencies to establish and navigate a unique and flexible regulatory pathway. Clearly, some uncertainties remain and are unavoidable, given the necessary use of surrogates (both for the virus and infected host) to establish tecovirimat efficacy and dose selection. Notably, the Animal Rule requires that a post-marketing clinical trial be done to verify tecovirimat's clinical benefit and assess its safety when such a study is feasible and ethical (eg, in the setting of a smallpox outbreak); a post-marketing requirement to this effect was issued at the time of tecovirimat's approval.[4] Although the FDA hopes smallpox will forever remain eradicated from the world, making it impossible to directly confirm tecovirimat safety and efficacy for its indicated use, the approval of tecovirimat will facilitate its use and clinical evaluation should this need arise.

Contributors

All authors contributed extensively in the regulatory review, independent analysis of submitted data, and ultimate FDA approval of tecovirimat. KMC-T, PRH, and AIS drafted the manuscript. S-YC, LM, JO'R, SS, DM, HG, and DB provided editorial advice on the manuscript.

Declaration of interests

We declare no competing interests.

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