FDA U.S. FOOD & DRUG ADMINISTRATION

July 31, 2018

The Honorable Lamar Alexander, Chairman
The Honorable Patty Murray, Ranking Member
Committee on Health, Education, Labor and Pensions
United States Senate
Washington, DC 20510

Dear Chairman Alexander and Senator Murray:

We are writing to share with you the Food and Drug Administration's (FDA or the Agency) current views on how it would implement the proposed expanded conditional approval pathway in H.R. 5554, the "Animal Drug and Animal Generic Drug User Fee Amendments of 2018." The Agency's staff were directed to review the possibility of expanding the conditional approval pathway by the previous reauthorization of the Animal Drug User Fee Act (ADUFA) and Animal Generic Drug User Fee Act (AGDUFA) programs in 2013, and we are prepared to implement the expansion of the pathway as outlined in H.R. 5554, if enacted, with appropriate regulatory caution and restrictions.

FDA currently has conditional approval authority for animal drugs intended to treat a minor species or for diseases or conditions in major species that would constitute a minor use, which was granted by the addition of section 571 to the Federal Food, Drug, and Cosmetic Act (FD&C Act) in 2004 by the Minor Use and Minor Species Animal Health Act (MUMS Act). To receive conditional approval, an animal drug sponsor must meet the same safety and manufacturing standards as a new animal drug for which full approval is sought under section 512. The main advantage of the conditional approval pathway for sponsors is that they can make their drug available after demonstrating a reasonable expectation of effectiveness. The pathway requires an annual review of the conditional approval to determine if the sponsor is making sufficient progress toward meeting the effectiveness standard for full approval.

FDA believes conditional approval offers a unique pathway to address specific challenges of certain aspects of veterinary medicine that human medicine does not face. Therefore, FDA does not believe this pathway would be suitable for human medical products. For example, variability in response to therapies among animals means that one product is not likely to meet the needs of all animals. Even within a single species (e.g., canine), it is well-documented that there can be significant variability among animal breeds in how drugs are metabolized (e.g., ivermectin is toxic for collies, but safe for other breeds). Despite the need, incentivizing new product development continues to be a challenge for the industry given the limited market for veterinary drugs. Based on experience, we believe this pathway would be used uncommonly, as a sponsor

must make a substantial investment of time and resources to obtain the conditional approval. In addition, the sponsor must be confident that they will ultimately be successful in meeting the substantial evidence of effectiveness standard required for full approval under section 512(b). FDA's review of its active pending animal drug products in various phases of development indicates that 16 products might qualify for the new pathway. FDA's best current estimate is that 12 to 20 animal drugs might seek conditional approval during the 10-year authorization period provided in H.R. 5554.

FDA has acted to withdraw conditional approval when sufficient progress towards meeting the effectiveness standard for full approval has not been met. For example, FDA withdrew the conditional approval of the drug Paccal Vet-CA1 in 2017, after it was conditionally approved in 2014, for this reason. Since the MUMS Act was enacted in 2004, only four drugs have received conditional approval, and FDA has only granted a full new animal drug approval to one of these drugs. We want to assure you that FDA will make certain there are appropriately defined parameters for this expansion of the conditional approval pathway, which will be developed through a public process.

The proposed expansion of the pathway in H.R. 5554 would allow certain animal drugs that are not intended to treat minor species or minor uses in major species to qualify for conditional approval, but only if they meet two key requirements. The first proposed requirement is that the drug must be "intended to treat a serious or life-threatening disease or condition or addresses an unmet animal or human health need." FDA considers serious or life-threatening diseases or conditions to be those that, if untreated, are likely to lead to an animal's death, such as congestive heart disease and lymphoma. FDA intends to define "unmet need" similarly to how the term is defined in FDA's Expedited Programs guidance for human medical products. FDA intends to provide more details to clearly define this first requirement in the guidance or regulation it would be required to issue.

The second key requirement for eligibility would be that "a demonstration of effectiveness would require a complex or particularly difficult study or studies." FDA believes use of the conditional approval pathway should and will be limited to situations in which effectiveness is in fact particularly difficult or complex to demonstrate, and would only be granted after demonstrating a reasonable expectation of effectiveness. FDA intends to consider whether the clinical end-points of the disease or condition are particularly difficult to evaluate. FDA also intends to consider factors such as the need of a sponsor to use complex adaptive or other novel investigation designs, real world evidence, and the difficulty of enrolling trials. To clarify the limited scope of new animal drug applications for which this pathway would be available, FDA intends to issue regulation to describe the elements it would consider in determining whether an effectiveness study would be difficult or complex to complete.

The proposed conditional approval expansion requires FDA to issue guidance or regulation by September 30, 2019, to clarify these criteria; FDA expects to finalize these documents before accepting applications for the expanded conditional approval pathway. We can assure you that FDA believes this expanded pathway should be used only in very limited cases, since its goal is to bring new veterinary therapies to market for which there have not been sufficient incentives to do so through the traditional new animal drug approval pathway. FDA does not believe the

conditional approval pathway should be available to new animal drugs that easily could use the traditional new animal drug approval pathway. If H.R. 5554 is enacted, we will keep your staff closely updated on our efforts to clarify in guidance and regulation the statutory restrictions on use of the expanded conditional approval pathway.

H.R. 5554 also contains language that will provide Congress the opportunity to reconsider conditional approval. The proposed pathway will sunset after 10 years, to coincide with the reauthorization of the user fee programs in 2028. In addition, the language requires a Government Accountability Office study to be completed prior to this date so that Congress, the Agency, and stakeholders can evaluate the expanded conditional approval pathway prior to its sunset. The sunset provision would create an incentive for the Agency and stakeholders to demonstrate that this pathway's implementation is appropriately implemented and judiciously utilized. Finally, H.R. 5554 further restricts this pathway by prohibiting any drug that contains an active antimicrobial ingredient from utilizing the expanded pathway.

In closing, we want to remind you that if H.R. 5554 is not reauthorized before August 1, 2018, we must initiate the process of adjusting animal drug review activities and the personnel engaged in those activities, including identifying and notifying 115 full time equivalent federal employee positions of a reduction in force no later than 60 days prior to their expected release. This could not only result in 115 full time employees being terminated, but would disrupt work and morale—not only for hundreds of other employees at the Agency's Center for Veterinary Medicine, but for their colleagues in other Agency centers as well.

We hope that we have been able to alleviate any concerns you have with the temporary, limited expansion of the Agency's existing conditional approval pathway for animal drugs in H.R. 5554, and that you will support timely passage of this bill to avoid any reductions in force and disruptions at the Agency. Again, you have our personal commitment to keep your staff informed as we implement this provision, if it is enacted.

Sincerely,

Scott Gottlieb, M.D.
Commissioner of Food and Drugs

Steve Solomon, DVM, MPH
Director, Center for Veterinary Medicine