

Submission: Agriculture and Environment Committee Inquiry: Hendra Virus (Equivac HeV®) Vaccine

Zoetis Australia Pty Limited

Executive Summary

Zoetis submits that:

1. Hendra virus is unique to Australia and has been responsible for over 90 horse fatalities and 4 human fatalities. The Hendra vaccine is the only known effective preventative measure. The vaccine is described by the Hendra Virus Inter-Agency Technical Working group as *“the single most effective way of reducing the risk of Hendra virus infection in horses [...] also to break the cycle of virus transmission from horses to humans.”*
2. The Hendra virus vaccine (Equivac HeV®) was developed through a partnership between Pfizer Animal Health (now Zoetis), the CSIRO and leading international research partners, to prevent the infection and death of horses and people, in response to an increase in Hendra Virus infections in horses and humans.
3. Equivac HeV was initially released under a Minor Use Permit, having satisfied Australian Pesticides and Veterinary Medicines Authority (APVMA) requirements for efficacy and safety. The APVMA's statutory requirements in relation to efficacy and safety are the same for Permits as for registration. The product was made available to veterinarians from 1 November 2012. It was registered on 4 August 2015 by the APVMA and since release over 440,000 doses have been administered to horses in Australia.
4. Equivac HeV has met all safety and efficacy criteria required by the APVMA, one of the world's most thorough regulators.
5. Equivac HeV has a reported adverse event rate of approximately 1 in every 350 doses given. The majority of the suspected adverse event reports collected since the product was released were collected under a *mandatory* adverse event reporting regime. The vast majority of the reported reactions are minor injection site reactions including pain and swelling at the site of injection and minor increases in body temperature which are transient and resolve without intervention.
6. The unique mandatory adverse event reporting conditions imposed on Equivac HeV for nearly 3 years provides detailed data as to the safety of the vaccine. That data confirms that the vaccine is safe and effective.

Background

1. The purpose of this document is to provide commentary on the following two terms of reference:
 - (a) the development, trials and approval processes; and
 - (b) the incidence and impact of adverse reactions by horses following vaccination and the reporting of adverse reactions.

Introduction

2. In 2010, following the fourth human death from Hendra virus, Pfizer Animal Health (now Zoetis) commenced work on the Hendra virus vaccine project. Many years of research into Hendra virus had been conducted by the CSIRO's Australian Animal Health Laboratory (AAHL), as well as by US agencies the Henry M. Jackson Foundation for the Advancement of Military Medicine, and the Uniformed Services University of the Health Sciences, which began researching Henipaviruses following the September 11, 2001 terror attacks. This was because the closely related Nipah virus had been identified as a potential biological weapon risk.
3. The researchers required a partner who could effectively manufacture the vaccine and effectively distribute the vaccine to the horse owning community. Zoetis, being the only manufacturer of equine vaccines in Australia, and with a manufacturing site in Melbourne, was able to bring large-scale manufacturing expertise to the project together with an established record of supplying cold chain vaccines to metropolitan and regional Australia.
4. The result of this project was the release of Equivac HeV on 1 November 2012. Equivac HeV is a 1mL injectable vaccine, which helps prevent Hendra virus infection in horses from four months of age. Equivac HeV is a 'subunit' vaccine, meaning it contains only a small part of the overall virus. It is not a live vaccine and cannot cause Hendra virus infection in horses. The vaccine stimulates the production of protective antibodies. If the horse is subsequently exposed to Hendra virus, the antibodies will bind to the virus, preventing it from establishing an active infection in the horse. Any viral particles bound to the antibody are then further processed by the immune system and eliminated.
5. Since the release of the vaccine, safety and efficacy of the vaccine has been the subject of some debate. On social media, in particular, some communities displayed negative views about vaccination *per se* and about the particular safety profile of the Hendra vaccine. Zoetis' respectful view of much of the commentary is that it is not supported by the science.
6. In 2014 [the Hendra Virus Inter-Agency Technical Working Group](#), comprising representatives from Biosecurity Queensland, Queensland Health, the Australian Veterinary Association and Workplace Health and Safety Queensland reported that the vaccine is:

the single most effective way of reducing the risk of Hendra virus infection in horses and provides a work health and safety and public health benefit by the vaccine's ability to not only protect horses from infection but also to break the cycle of virus transmission from horses to humans.

Term of Reference 1: the development, trials and approval processes

7. The Hendra virus vaccine project was initiated in July 2010 with the objective to develop a safe, efficacious and high quality vaccine as an aid in the control Hendra virus infection in horses. At the time of writing, there have been approximately 55 incidents of Hendra virus infections involving over 90 horses (all deceased) and 7 humans (4 deceased).
8. The project was undertaken in collaboration with external parties including the Henry M. Jackson Foundation for the Advancement of Military Medicine (USA), the

Uniformed Services University of the Health Sciences (USA) and the CSIRO's Australian Animal Health Laboratory (AAHL).

9. The initial requirement was the identification of an antigen (viral component) that had the ability to trigger immunity to Hendra virus infection if injected as a formulated vaccine into a horse. It was found that a particular virus glycoprotein (G protein) provided such protection against Hendra virus. The importance of the identification of the specific G protein is that it allowed the development of a vaccine that did not require use of live Hendra virus at any stage in the manufacture of the vaccine. A licensing agreement was secured with Henry Jackson Foundation for the use of this glycoprotein in vaccine development.
10. By April 2012, Pfizer Animal Health had completed required safety and field trials for the vaccine. **Safety studies** involve horses being immunised with the vaccine in overdose and repeat dose studies to monitor the general health of the horse following vaccination as well as detailed examination of the vaccine injection site for any prolonged adverse reactions. **Field trials** are performed to ensure that the vaccine performs appropriately from both an efficacy and safety perspective in larger numbers of horses than can be accommodated during pivotal efficacy and safety studies, which generally involve much lower numbers of animals. At this time Pfizer also completed an APVMA submission for a Minor Use Permit to allow the use of the product prior to product registration since the data had already demonstrated acceptable efficacy and safety parameters were met. It is important to note that the efficacy and safety trials conducted in support of the Minor Use Permit **were exactly the same trials that were submitted in support of product registration.**
11. In August 2012, a Minor Use Permit was granted and manufacturing of the commercial vaccine commenced. The product was released for use by veterinarians on 1 November 2012 and continued to be available under permit until August 2015.
12. In May 2013, Zoetis submitted the registration data package to support full product registration and following an extensive evaluation period, the APVMA published the initial assessment of the registration dossier submitted by Zoetis in Gazette No. APVMA 12, Tuesday, 17 June 2014 (<http://apvma.gov.au/node/11226>). As with all product registrations involving a new active ingredient, this was to inform the public of the APVMA's findings and to invite public comment on APVMA's proposal to register the vaccine. **This publication confirmed that the APVMA was "satisfied that the data supporting the efficacy and safety of the product adequately demonstrate that this product is likely to be safe and effective under Australian conditions when used according to label instructions."**
13. On 4 August 2015, the APVMA registered the Hendra virus vaccine under the trade name, EQUIVAC HEV HENDRA VIRUS VACCINE FOR HORSES ([APVMA Registration number: 68996](#)).
14. In September 2015, following completion of safety and field trials for a new claim for use of the product in pregnant mares, Zoetis submitted an application to vary the registration of the vaccine to have this new claim placed on the product label. On 20 January 2016 the APVMA approved the use of Equivac HeV for use in pregnant mares.
15. Following advice from APVMA in relation to a previous submission for annual boosters, i.e. 12 months duration of immunity, in November 2015 Zoetis submitted additional field trial data to support a new application for annual boosters, The proposed usage pattern for the vaccine is two initial priming doses 4-6 weeks apart,

followed by a booster 6 months after the second priming dose, followed by annual booster vaccinations on an ongoing basis.

16. As of the time of writing, the APVMA response to the November 2015 application was still pending, with a response expected before the end of 2016.

Term of Reference 2: the incidence and impact of adverse reactions by horses following vaccination and the reporting of adverse reactions

17. Since the release of the vaccine to 30 March 2016 over 440,000 doses of the vaccine have been administered. Under the terms of the Minor Use Permits in force between 1 November 2012 and 3 August 2015 all doses of Equivac HeV administered were required to be recorded in Zoetis' Hendra Vaccine Registry. It was also a condition of the Minor Use Permits for all accredited veterinarians to report all adverse events to Zoetis within 48 hours of them being made aware of them. The Permits also required Zoetis to report all suspected adverse events to APVMA within 48 hours of being made aware of the suspected adverse events by veterinarians or horse owners.
18. Up until the end of March 2016 the total number of suspected adverse reactions reported which Zoetis assessed as 'Probably' or 'Possibly' related to the use of the vaccine was 1,255. This translates to an approximate incidence of reactions to 1 in every 350 doses or around 0.3% of doses administered. The vast majority of these reactions involve clinical signs mentioned within the product label as potential side-effects of the vaccine, which are similar in nature to those that would be expected in a human patient receiving, for instance, a tetanus vaccination.
19. The incidence of local adverse events reported for Equivac HeV is much lower than the rate that has been identified to occur in humans after tetanus vaccination. The [World Health Organisation has stated of tetanus vaccination](#) that, "Local reactions are common and have been reported to occur in 50-80% of vaccine recipients who receive a booster dose."
20. Zoetis believes that a number of unique factors are relevant when analysing the reported incidence of suspected adverse events to Equivac HeV:
 - (a) under the terms of the Minor Use Permit from the 1 November 2012 to 4 August 2015, a regime of *mandatory* adverse event reporting was imposed. The Minor Use Permit required veterinarians to report ANY suspected adverse event to Zoetis within 48 hours of being made aware of it, while Zoetis in turn was required to report any and all suspected adverse events reported to Zoetis to the APVMA within 48 hours. This requirement is in contrast to requirements in place for all other APVMA registered products, where as far as Zoetis is aware, operate under a voluntary or *spontaneous* adverse event reporting regime. This means that while it is good practice for veterinarians and the general public to report adverse events for other products neither party is under an obligation to do so, and failure to report an adverse event does not carry any further consequences. Global pharmacovigilance norms (pharmacovigilance being the collection and analysis of data from adverse events collected after a human or animal medicine is approved) also utilise data obtained only from *spontaneously* reported adverse events and are required to ignore data generated under a *solicited or mandatory* regime. This is because it is accepted that incidence data will be overstated when data is collected under solicited or mandatory regimes.

In an attempt to understand and quantify the impact on **reported incidence rates under the mandatory regime for the Hendra vaccine** when compared to a **spontaneous adverse event reporting regime**, Zoetis examined data from the European Union where a Zoetis product was subjected to an unusually large field trial that was conducted prior to full product launch, in which adverse event reporting was *solicited* (i.e. pet owners and veterinarians were *requested* to supply all adverse event reports as part of the field trial, but reporting was not *mandatory*) compared to the subsequent spontaneous reporting regime after the product was released more widely into the market. It was found that the rate of adverse events reported under the solicited adverse event reporting regime were 60-80 times higher than the rate of adverse events reported under the post-launch spontaneous regime. Zoetis' view is that it would be expected that under a *mandatory* adverse event reporting regime (given that APVMA could seek to apply penalties to veterinarians and Zoetis for non-compliance), the difference in the rate of adverse event reporting compared to a spontaneous regime will be even higher than when comparing *solicited* and spontaneous adverse event reports;

- (b) there has been significant community interest in and awareness of adverse event reporting for this product. Partly this has been due to Zoetis' diligence in implementing the requirements of the APVMA Minor Use Permit. It is also partly due to the fact that the Hendra virus is responsible for significant fatalities. Also, the APVMA has created a number of pages on the APVMA website dedicated to the product, one of which specifically details the number and clinical signs in relation to adverse events reported for the Hendra vaccine while it was available under APVMA Minor Use Permit.

The main Hendra information page can be found here:
<http://apvma.gov.au/node/12871>.

The page detailing the type and incidence of adverse events can be found here: <http://apvma.gov.au/node/15786>;

- (c) in addition to the pages above on the APVMA website, social media has played a significant role in informing and educating end-users around routes for adverse event reporting; and
 - (d) as well as social media, the Hendra vaccine has attracted significant mainstream media focus, with a number of reports focussing on the topic of adverse events. Zoetis is not aware of other equivalent products being subjected to similar mainstream media interest.
21. Zoetis is of the view that mandatory adverse event reporting has made veterinarians and the general public more aware of avenues for reporting adverse events, and that this will continue to impact the rate at which suspected adverse events are reported until reporting habits revert to the norms that exist for other products. Given these circumstances, the rate at which adverse events are reported for this product is further confirmation of the safety of the product. It is Zoetis' belief that were it not for these unique factors impacting on the rate of reporting, the reported incidence of adverse events would be lower than the rate of 0.3% described above.
22. It is important to keep in mind that the assessment and classification of any suspected adverse event is not only assessed by Zoetis, but also determined independently by APVMA through its own assessment process. It is also important to highlight that APVMA's and Zoetis' classifications of 'possible' or 'probable' do not

definitively mean that the vaccine is responsible for the symptom reported. Cases classified as 'possible' mean the vaccine was identified as one of a number of **equally plausible causes**. Cases deemed to have a strong likelihood of association with the use of the vaccine are given a classification of 'probable'.

23. The APVMA has classified a small number of reported horse deaths as 'possibly' due to vaccination. The definition of 'Possible' means the vaccine is one of a number of **equally plausible causes** of the horse's death in the opinion of the APVMA. The classification does not indicate any particular likelihood that the vaccine caused the symptom. If the vaccine was the most likely cause of death it would have been classified as 'probable'.

Conclusion

24. Zoetis has responded to overwhelming government, industry and community demand for a vaccine to save the lives of people and horses and to help to preserve the livelihoods of people working in industries directly affected by this deadly virus.
25. The vaccine was developed in conjunction with the CSIRO and highly respected international institutions.
26. The label advice and warnings in relation to the use of Equivac HeV have been approved by the APVMA and allows horse owners in association with their veterinarian to make an informed decision about whether or not to vaccinate individual horses.
27. Zoetis believes that the benefit of vaccination with Equivac HeV far outweighs any risk.

About Zoetis

Building on more than 60 years of experience in animal health, Zoetis discovers, develops, manufactures and markets veterinary vaccines and medicines, complemented by diagnostic products, genetic tests and a range of services. Zoetis serves veterinarians, livestock producers and people who raise and care for farm and companion animals with sales of its products in more than 100 countries.