

CARE AND OVERSIGHT OF  
HORSES MANAGED FOR THE  
COLLECTION OF  
PREGNANT MARES' URINE  
(PMU)

A White Paper Prepared by  
The Equine Ranching Advisory Board  
June 2014

# Equine Ranching Advisory Board Report

## June 2014

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## **ACRONYMS**

AAALAC – Association for the Assessment and Accreditation of Laboratory Animals

AAEP – American Association of Equine Practitioners

APHIS – Animal and Plant Health Inspection Service

BEVA – British Equine Veterinary Association

CanFACT – Canadian Farm Animal Care Trust

CCAC – Canadian Council on Animal Care

CVMA – Canadian Veterinary Medical Association

ERAB – Equine Ranching Advisory Board

FARMS – Field Audit Ranch Management System

ILPH – International League for the Protection of Horses

LER – Linwood Equine Ranch

NAERIC – North American Equine Ranching Information Council

PMU – pregnant mares' urine

RSPCA – Royal Society for the Prevention of Cruelty to Animals

USDA – United States Department of Agriculture

WSPA – World Society for the Protection of Animals

***Throughout this paper corporate activities are referenced to Pfizer. However, the reader should understand that initiatives made prior to November 2009 in the equine ranching network occurred under the entity name Wyeth Pharmaceuticals.***

## EXECUTIVE SUMMARY

The role of the Equine Ranching Advisory Board (ERAB) is to advise Pfizer Brandon on the management, husbandry and welfare of horses used in pregnant mares' urine (PMU) collection. The ERAB offers the following report to the American Association of Equine Practitioners (AAEP) to summarize more than 15 years of oversight of the PMU network.

Veterinarians representing the AAEP, the Canadian Veterinary Medical Association and the International League for the Protection of Horses have previously visited a broad spectrum of equine ranches engaged in the collection of PMU. The purposes of those visits were to observe first-hand the health and welfare of the horses involved in production of the Premarin® family of products, estrogen replacement medications derived from PMU, and to confirm Pfizer's field application of the Continuous Improvement Program in horse care. The report entitled, "Equine Veterinarians' Consensus Report on the Care of Horses on PMU Ranches" concluded that ranchers took pride in their animals, and that Pfizer showed a commitment to continuing to improve the standards of equine welfare on the ranches. The "Consensus Report" veterinarians identified specific areas for scientific research and educational initiatives for Pfizer.

As a follow-up to the report, the ERAB supports the following statements:

- The current *AAEP Position on the Management of Mares Utilized in the Pregnant Mare Urine (PMU) Collection Industry (2010)* which states, "Through on-site investigations and peer review of ongoing research, the AAEP believes the collection of urine from pregnant mares and care of their offspring as prescribed by the recommended *Code of Practice*, represents responsible management of horses to produce a commodity for the benefit of mankind that should not result in abuse, neglect or inhumane treatment of horses."
- The use of horses by Pfizer to produce a product that benefits human health is justified and warranted as long as the health and welfare of the horses under Pfizer stewardship meets or exceeds science-based, informed veterinary criteria for management of these horse herds.
- Science-based horse management recommendations should continue to be utilized in establishing standards for equine ranching and PMU production.
- The Continuous Improvement Program must serve as the guiding doctrine for all equine ranching and PMU production activities.
- Herd health reviews of equine ranches by independent, certified, veterinarians should continue to be a necessary component of a system of checks and balances ensuring the health and welfare of horses used for PMU production. Reviews should be based on the standards described in the *Recommended Code of Practice for Horses on PMU Ranches*.

- Linwood Equine Ranch, a CCAC-approved research and working PMU ranch, is the only facility in the world that specifically conducts applied research into the care and welfare of PMU horses and provides the quality assurance of oversight of horses in the PMU industry. Linwood Equine Ranch provides research-based recommendations important to the continued improvement of horse management on equine ranches and supports the requirement for peer reviewed research which is a basic condition of the American Association of Equine Practitioners' "Position on the Management of Mares Utilized in the Pregnant Mare Urine (PMU) Collection Industry" as revised by the AAEP board of directors in 2010.
- Rancher assistance programs are essential in supporting the continued marketing and placement of horses into productive markets. This is a role the North American Equine Ranching Information Council (NAERIC) has played and continues to play. NAERIC programs create value-added marketing opportunities for the continuous improvement in the sale of horses that are produced as a result of estrogen production. It is recognized that not all horses can be guaranteed to go to productive markets; however, the effort to identify productive markets is paramount to the continued placement initiatives that have been developed.
- The Marketing Assistance Program should continually be reviewed in concert with Pfizer Brandon to ensure that monies allocated to the program directly benefit placement of horses. Allocations to this program need to be reviewed to address the inability of the fund to cover all requested reimbursements. The electronic tracking of horses utilizing the program provides documentation that horses are being placed in productive markets.
- It is incumbent upon all divisions of Pfizer to acknowledge that horses are produced as a result of the extraction of estrogens for medicinal purposes. The company is responsible to adequately and universally support the continued placement of horses via reputable and recognized markets, utilizing sufficient and appropriate resources.
- The Equine Ranching Advisory Board, or an equivalent, should continue to provide oversight and receive reports on activities pertinent to equine ranching and PMU production.
- No lesser standard for horse care and oversight should be accepted from any other organization participating in equine ranching and PMU collection as those described herein.
- To ensure oversight, the equine ranching industry should continue to report to the American Association of Equine Practitioners as appropriate.

## **PURPOSE**

Socio-ethical concerns about the use of animals in human-related activities have undergone a profound change over the past several decades. The appropriateness of traditional uses of horses for recreation, sport, competition and entertainment continues to be debated with increasing attention paid to determining if the activity is deemed non-essential or essential. In the early 1990s, ranchers residing in Canada's prairie provinces of Alberta, Manitoba and Saskatchewan and the state of North Dakota came under scrutiny by animal activist groups because they collected pregnant mares' urine (PMU). Estrogens are extracted from PMU by a leading pharmaceutical company to produce hormone therapies for post-menopausal women. The debate concerned the appropriateness of using horses, and the methods employed, to produce a commodity for the benefit of mankind.

In November 1996 three equine veterinarians representing the American Association of Equine Practitioners (AAEP), the Canadian Veterinary Medical Association (CVMA) and the International League for the Protection of Horses (ILPH) visited a broad spectrum of equine ranches engaged in the collection of PMU. The purpose of the visits was to observe the health and welfare of the horses involved in the production of Premarin<sup>®</sup>, the estrogen replacement medication extracted from PMU, and to confirm Pfizer's field application of the Continuous Improvement Process. The report, "Equine Veterinarians' Consensus Report of the Care of Horses on PMU Ranches" was issued in May of 1997.

In a book devoted to equine welfare, one of these three international experts described the welfare of horses in the PMU industry (Messer, 2011). The following report, prepared by the Equine Ranching Advisory Board, describes in comprehensive detail the continuous improvement activities made in horse research and marketing in the equine ranching industry over more than 15 years.

## INTRODUCTION

The Equine Ranching Advisory Board (ERAB) is a multidisciplinary group with equine expertise in: medicine, surgery, physiology, behavior, reproduction, biosecurity and nutrition. Its function is to advise Pfizer management and its Director, Veterinary Research / Field Compliance regarding relevant basic and applied research with respect to horses used in PMU collection and their management and husbandry. ERAB was created in 2003 through an amalgamation of two separate entities formed in 1995, the Equine Management Group and the Equine Advisory Board. These two groups were formed to assist Pfizer in the management of horses in the PMU network, and to assist the managing veterinarian of Linwood Equine Ranch, a Pfizer PMU research facility, with designing research studies and implementing research conclusions.

ERAB continues in this capacity and also assists in the prioritization of scientific/educational goals of Linwood Equine Ranch, protocol development, study design and implementation, preparation and review of final reports and research articles for publication. They also give advice and counsel to Pfizer on various issues associated with the equine ranching industry.

The current *AAEP Position on the Management of Mares Utilized in the Pregnant Mare Urine (PMU) Collection Industry (2010)* states “Through on-site investigations and peer review of ongoing research, the American Association of Equine Practitioners believes the collection of urine from pregnant mares and care of their offspring as prescribed by the recommended ‘Code of Practice,’ represents responsible management of horses to produce a commodity for the benefit of mankind that should not result in abuse, neglect or inhumane treatment of horses.”

This position statement was formulated with direct application to the equine ranching network under contract to Pfizer. Recently, ERAB has become aware that there are potential other entrants into the PMU collection industry whose practices may be dissimilar to those described in the position statement. The following white paper was created to substantiate the practices of ranchers under contract with Pfizer concerning the care of horses used in PMU collection.



## **BACKGROUND**

### **History of Equine Ranching**

Prior to the 20<sup>th</sup> century, no therapy was available for the treatment of symptoms of menopause in women (Stefanick, 2005). Many interim therapies including extracts of bovine amniotic fluid, human pregnancy urine, and human placental extracts were used until 1939 when Ayerst scientists extracted conjugated equine estrogen (CEE) from PMU. The CEE extract was developed into the human hormone therapy, Premarin<sup>®</sup>, which was first marketed in Canada in 1941. The following year it was approved for use in the United States. In 1943, the American Home Products Corporation (AHPC) purchased Ayerst, McKenna & Harrison, Ltd., later shortening the name to Ayerst Laboratories and subsequently merging it with Philadelphia-based Wyeth Laboratories in 1987. Pfizer acquired Wyeth in 2009.

Initially, the company contracted farmers in rural Quebec, near their manufacturing plant in Montreal. As Premarin<sup>®</sup> use increased, additional ranchers were sought in Ontario, upstate New York and Vermont. However, in the 1960s as menopause was discussed more openly, Premarin<sup>®</sup> usage increased significantly. Company forecasts indicated the increasing demand could only be met by expansion to the western Canadian prairies where horses and pasture land were plentiful. As a result, PMU ranches made the transition from eastern Canada to the provinces of Alberta, Manitoba and Saskatchewan, and the state of North Dakota.

Rancher numbers increased until 2003 when Wyeth Pharmaceuticals reduced the rancher network due to a combination of factors including improvements in manufacturing and inventory management, a shift to lower estrogen dosage Premarin<sup>®</sup> and reduced demand as result of the Women's Health Initiative (WHI) study. Rancher and horse numbers were further reduced through 2013.

The PMU equine ranchers' network is comprised of 19 independent ranches and Linwood Equine Ranch that collect urine from approximately 1,300 pregnant mares in the provinces of Manitoba and Saskatchewan, Canada. The provinces' average annual temperature is +2.6 °C. Sub-zero temperatures occur from November to April averaging -12°C. January is the coldest month in Manitoba with an average high of -12.7 °C and an average low of -22.8°C (Statistics Canada, 2007). The period from November through February coincides with the typical PMU collection season when mares are housed in temperature-controlled barns. For the remainder of the year they are maintained on extensive pastures.

The ranches are sparsely located across these two provinces. The proximity between any two ranches ranges from 4 to 110 km. The sparse horse population has at least 3 benefits:

1. Biosecurity – physical separation by distance and geography effectively isolates horses on PMU ranches from neighboring horses.
2. Localization of disease risk – disease risks differ between Saskatchewan and Manitoba; e.g., anthrax occurs in circumscribed regions in each province.
3. Extensive husbandry of small bands of horses – pastures and paddocks can be as large as 160 acres or more which reduces the concentration of disease-causing agents and the exposure of horses to disease typically seen in confined cover.

The breed distribution of mares is 50% draft horses, principally Percheron and Belgian, 42% light breeds mainly Quarter Horse and 8% cross-bred mares. All stallions used in the industry are registered; 93% of mares are registered. The exceptions are cross-bred mares used in the Performance Horse breeding program. Each horse on every ranch is uniquely identified. Health records are kept for all horses including routine herd health programs and medical treatment of the horse.

### **PMU Ranching and the Veterinary Consensus Report**

The use of horses to collect PMU came under attack in the early 1990s with various allegations of problems with watering, reproductive management, turnout and foal sales. As a result, several welfare organizations: CanFACT, USDA, RSPCA, WSPA, AAEP, ILPH, BEVA and CVMA were invited to tour PMU ranches.

The CVMA, ILPH and AAEP were invited in 1996 to provide a report to Pfizer on the conditions of PMU ranches. The report entitled “Equine Veterinarians, Consensus Report on the Care of Horses on PMU Ranches” was filed by Drs. Nat Messer (AAEP), Art King (CVMA) and Colin Roberts (ILPH) following a November 1996 inspection of 25 ranches and concluded “The ranchers took pride in their animals, and Wyeth-Ayerst showed a commitment to continuing to improve the standards of equine welfare on the farms” (King et al., 1997). The consensus team identified specific areas for scientific research and educational initiatives for Pfizer.

The science-based research initiatives suggested in the consensus report were:

1. Determine optimal exercise requirements for stabled horses, particularly any associated impact on the lower limbs.
2. Investigate materials and designs used in the construction of stalls and floors, particularly to minimize lower limb edema and injury.

3. Determine optimal frequency for watering and whether constant watering provides any physiological and psychological benefit or leads to significant husbandry disadvantages.
4. Investigate options for free-movement collection system.
5. Investigate factors that might affect estrogen production such as breed and nutrition.
6. Determine need for, and range of, grooming requirements.

The consensus team also recommended the following administrative and educational initiatives:

1. Continue to review the *Code of Practice* standards regarding care and management of horses as new information is obtained from ongoing research.
2. Work to assure consistent level of detail in independent veterinary reporting through liaison with veterinarians, and education concerning veterinary care standards for PMU industry.
3. Review standards for, and conditions of, turnout areas.
4. Consider changes to the payment process for the Independent Veterinary Review Program.
5. Initiate program for rotation of field inspectors to cover farms in different areas.
6. Develop continuing education on equine health for all farm personnel through creation of workshops, audio-visual and education materials, and sharing of “best practices” related to equine and PMU management.

Pfizer used these suggestions as a guideline to direct controlled and demonstrational research at the company’s Linwood Equine Ranch and studies at other institutions. These scientific activities will be described in detail in the following order:

1. *Recommended Code of Practice for the Care and Handling of Horses on PMU Ranches*
2. Pfizer Field Operations and FARMS audit software
3. Herd Health Reviews by Independent Veterinarians
4. Linwood Equine Ranch (LER) – Facility and Role

5. LER Research – projects, conclusions and application to ranching practices
  - a) Watering
  - b) Turnout/Exercise
  - c) Nutrition
  - d) Alternative Collection Methods
  - e) Husbandry and Management
  - f) Veterinary Testing
  - g) Equine Arteritis Testing
6. North American Equine Ranching Information Council, Inc. (NAERIC)

## **QUALITY ASSURANCE IN THE CARE AND HEALTH OF HORSES IN EQUINE RANCHING**

### **The Recommended Code of Practice for the Care and Handling of Horses on PMU Ranches**

*The Recommended code of Practice for the Care and Handling of Horses on PMU Operations (Code of Practice)* was first published in 1990 by the province of Manitoba (Canada). A committee of ranchers, veterinarians and government officials integrated preferred and scientifically acceptable practices for horse keeping. Subsequently, in 1998, the *Recommended Code of Practice for the Care and Handling of Farm Animals: Horses* was developed by Canadian Agri-Food Research Council to which the equine ranching *Code of Practice* was appended. Both codes are amended regularly to keep up to date with science in the care of horses. The sixth revised *Recommended Code of Practice for Horses on PMU Ranches* and the second edition of the *Code of Practice for the Care and Handling of Equines* were published in 2013. The *Code of Practice* is endorsed by the Minister of Agriculture, Food and Rural Initiatives in Manitoba, and the Minister of Agriculture in Saskatchewan, the two Canadian provinces where PMU production occurs with ranchers under contract with Pfizer.

The *Code of Practice* is a comprehensive and objective guideline for equine ranchers to apply the best management and husbandry care for horses in PMU collection. Although written as a voluntary guideline, the contract between rancher and the contracting company specifies compliance with the Code. Thus, Code adherence is a mandatory requirement for PMU ranchers. Compliance with the Code is assessed by certified veterinarians and recorded in the Herd Health Review of Equine Ranches. Field Auditors for the contracting company, Pfizer, also use the *Code of Practice* as a reference for monthly ranch audits.

### **Pfizer Field Operations and FARMS Audit Program**

The current, 2014, Pfizer Field Operations team is comprised of auditors trained in horse husbandry and welfare who have a minimum of ten years experience in farm audits. Audits of each ranch are conducted monthly throughout the year. Audit standards are based on specific contractual obligations and adherence to the *Recommended Code of Practice for the Care and Handling of Horses on PMU Ranches* (2013). These audits are cross-referenced with the certified veterinary reviews (Herd Health Reviews of Equine Ranches).

All farm audits are input into a unique software program, called FARMS (Field Audit Ranch Management System), developed specifically for Pfizer for the purpose of PMU ranch audits. Completed, signed audit documents must be reviewed weekly and undergo an approval process after which they are electronically filed in the audit database. The Director, Veterinary Research/Field Compliance, participates in the review and approval process and is alerted prior to weekly reviews if there are any concerns, whether facility or horse. A blank current field audit form is attached (see Attachment 1).

### **Herd Health Review by Independent Veterinarians**

Herd health reviews of horses and facilities are unique to equine ranching. No other farm animal industry undergoes such regular scrutiny. By contract with Pfizer, equine ranchers are required to have a certified, licensed veterinary practitioner provide a standard, comprehensive review of their facilities, horses, and horse care twice during the PMU collection season. The herd health review form must be returned to Pfizer for review by the company veterinarian within one week of completion. Data from the herd health review are catalogued and cross-referenced with the monthly Field Operations audit. Field auditors investigate any out-of-compliance event noted in the herd health review.

The origin of the herd health review by private veterinarians was based on the concept that veterinarians are qualified experts in assessing animal well-being. In 1995, a committee of Manitoba private practitioners and government veterinarians developed the herd health review program for the PMU industry. The certified veterinarian assesses each herd's health program (vaccination, parasite control, and reproduction), clinical medical and surgical records, biosecurity, diet, watering and husbandry. The review process is an opportunity for the attending veterinarian to advise the rancher about husbandry and veterinary programs.

The herd health review has undergone several iterations since 1995. The 4-page assessment form is reviewed regularly by the Herd Health Review committee (a Sub-committee of the PMU Code of Practice Committee). An example of the Herd Health Review of Equine Ranches is given in Attachment 2.

All veterinarians conducting herd health reviews of PMU ranches must be certified by attending continuing education seminars organized by Pfizer. These seminars provide current veterinary and management practices expected on equine ranches and are used to help standardize the review process. The ratio of individual veterinarians that complete herd health reviews is about one veterinarian for every two equine ranches. This ratio reassures against bias and provides a good cross section of veterinary expertise and knowledge.

## **EFFECTIVENESS OF THE AUDIT SYSTEM**

The herd health review and FARMS audits have confirmed that the health care of the horses on equine ranches meets or exceeds most other horse industry constituencies. As a point of reference, the health care data and activities derived from herd health reviews and the monthly Pfizer audit of equine ranches (2013-14) was compared to the National Animal Health Monitoring System (NAHMS, 1998, 2005) (Table 1). The NAHMS study is an extensive survey of horse health and management conducted in 28 states in the USA in 1998 and 2005.

The data confirm that 100% of equine ranches are visited by veterinarians at least three times per year to comply with mandatory programs such as the herd health review and pregnancy examination. Thus, veterinary care on equine ranches exceeds that of the U.S. household-owned horse population, as reported by the American Veterinary Medical Association, Centers for Information Management, in their most recent (2012) report, which stated that “46.28% of U.S. household-owned horses did not receive a visit from a veterinarian.”

By comparison equine breeders or all respondents surveyed in the NAHMS study reported that only 17.8% had computerized health records, 8.1% analyzed feed, 68% bought vaccines from veterinarians, and 35.3% used manure to fertilize their croplands.

Table 1. Comparison of PMU ranch programs with similar activities by breeding farms that reported data in the NAHMS (2005) study

Item	PMU ranches	NAHMS <sup>1</sup> (breeding or all operations)
Visits by veterinarians	100% (3X/yr)	46.3% ( 1X/yr)
Computerized health records	100%	17.8% ± 1.9
Feed or pasture analysis	100%	8.1 %± 0.5
Fecal tests for parasites	45%	13.5 % ±0.7
At least one EVA test during past 12 months (% operations)	100%	Not available
Any vaccine to any resident equids during the previous 12 months (% operations)	100%	89.7% ±1.6
Veterinarian primary source of vaccines	100%	68%
Biosecurity precautions (disinfect; clean coveralls, boot change, etc)	100%	33.2% ±2.23
Contact with		
poultry on premises	0%	18.1% ± 1.9
Ruminants on premises	35%	36.7% ± 1.9
Horses fed grain/concentrate during previous 12 months (% operations)	100%	90.1%
Well water predominant drinking water source	100%	57.5% ± 0.9
Manure management – compost/applied on field where livestock may graze	100%	35.3% ± 2.3

<sup>1</sup> Source: American Veterinary Medical Association, Centers for Information Management, 2012 and National Animal Health Monitoring System (1998, 2005).

## CHECKS AND BALANCES IN THE EQUINE RANCHING INDUSTRY

Equine ranching for PMU production has more checks and balances to ensure animal care and welfare than any other livestock industry, making it one of the most regulated and closely inspected equine-related activities in the world. Multiple layers of governance in disease control and animal welfare including corporate audits, independent veterinary herd health reviews, legislative and contractual obligations are used to ensure appropriate care of horses used in PMU collection.

### Legislative Oversight

Compliance with applicable agricultural regulations of the Canadian federal government and provincial governments of Manitoba and Saskatchewan, Canada, are required. Specific federal acts germane to the PMU industry are the Health of Animals Act, the Reportable Diseases Act, and the Health of Animals Regulation. The Manitoba Animal Care Act requires that horses used for PMU collection must be kept in accordance with the *Code of Practice for the Care and Handling of Horses on PMU Operations*.

All equine diseases identified in the Reportable Diseases Act (Canada) must be reported to Pfizer, and by law, veterinary authorities of the Canadian government must be notified immediately or the owner will risk severe penalty.

### Pfizer / Rancher Contract

An important governance entity is the contract signed between the PMU (equine) rancher and Pfizer Global Supply, Brandon (Pfizer Brandon). The contract has specific clauses requiring adherence to the equine codes of practice, federal and provincial regulations and inspections by veterinarians and Pfizer Field Operations auditors. The contract also has specific, robust animal care requirements for horse care which exceed those given in the two equine Canadian Codes of Practice which apply to horses on equine ranches: the “*Recommended Code of Practice for The Care and Handling of Horses on PMU Ranches (2013)*,” and, federal or Canadian government “*Code of Practice for The Care and Handling of Equines (NFACC, 2013)*”.

Specific contract requirements are:

1. *Mandatory vaccination.* By Pfizer contract, all pregnant mares used for PMU collection must be vaccinated using West Nile Virus vaccine and Equine Influenza Virus vaccine in addition to vaccinations noted in the *Code of Practice*. Each rancher must sign a certificate verifying the date the vaccine was administered, the vaccine name, the vaccine batch and the purchase invoice number for the vaccine. Other herd health vaccination programs are directed by the ranch’s attending veterinarian who chooses vaccines to prevent specific diseases in a high-risk region.



2. Reportable disease declaration. Ranchers must notify Pfizer of any reportable disease (e.g. Equine Infectious Anemia or Vesicular Stomatitis), immediately notifiable and/or annually notifiable disease, in any owned or leased horses on the ranch within one week of diagnosis.
3. Turnout program. Mares must be turned out according to their individual requirement based on the assessment by the rancher, field auditor and/or veterinarian. Horses, at minimum, must be turned out bi-weekly and each mare's turnout must be recorded in a Pfizer logbook.
4. Mandatory feed testing. Feeds provided to mares used in PMU collection must be analyzed. Analysis of feeds is conducted by a commercial feed testing laboratory and paid for by Pfizer. Ration formulation is not mandatory but all rations are reviewed either by the attending or company veterinarian(s) to ensure that adequate nutrients are supplied. Rations for young horses are also reviewed. Ranchers must sign a certificate of quality of feed supplements used for pregnant mares which attests that no feed supplement contains animal by-products.
5. Hoof care requirements. All mares used for PMU collection must receive farrier attention a minimum of twice per year. Hoof care is evaluated monthly by Pfizer field auditors and recorded in FARMS, the farm audit program. During the PMU collection season, hoof care is reviewed and recommendations, with respect to farrier requirements, are recorded by veterinarians in the Herd Health Review.
6. Pregnancy evaluation. Ranchers agree to have a manual pregnancy check conducted by a licensed veterinarian prior to PMU collection.
7. Testing for the presence of Equine Arteritis Virus (EAV) in breeding stallions. All new stallion additions to resident herds must be kept quarantined until the stallion is sero-tested for the presence of EAV. Ranchers must provide written evidence that stallions are verified seronegative or semen-negative for EAV before they can be used for breeding.
8. Horse and foal marketing. Horses should be placed in a productive market with guidance from North American Equine Ranching Information Council, (NAERIC).

### **Multiple Levels of Inspection**

Equine ranches have undergone many reviews conducted by individuals representing animal welfare/veterinary group including but not limited to: CanFACT, USDA, RSPCA, WSPA, AAEP, ILPH, BEVA and CVMA (1993 - 96; 2002, 2006). Auditors from the Pfizer Field Operations team in Brandon, MB review ranches monthly throughout the year whether horses are in the barn or on pasture. Veterinarians review the ranchers' horses at a minimum of three times per year: two Herd Health Reviews and one mandatory pregnancy evaluation. These veterinarians have been certified through a program developed by the *Recommended Code of Practice for the Care and Handling of Horses on PMU Ranches* Committee, and they have received continuing education credits from their provincial veterinary associations. Under the Animal Care Act, authority for the investigation of public concerns regarding animal neglect, abuse or cruelty is vested in the Veterinary Services Branch of Manitoba Agriculture. Department staff has the authority to investigate complaints. Similar authorization exists for the Saskatchewan Society for the Prevention of Cruelty to Animals (SPCA) under the Saskatchewan Animal Protection Act.

## **WELLNESS AND CARE PROGRAMS**

### **Linwood Equine Ranch - Facility and Purpose**

Linwood Equine Ranch is a 969 acre research and pasture facility owned by Pfizer. It was an existing family-owned PMU ranch purchased in 1995 to function as a model working PMU ranch. The ranch was customized to conduct applied research into continuous improvements in horse husbandry, and the care and welfare of horses in the equine ranching network. A Pfizer veterinarian and research staff manage the ranch and research studies. Horse care is provided by Pfizer support staff.

Linwood is the only facility in the world that specifically targets research into the husbandry of horses in equine ranching. Although the specific emphasis of research is on the care and welfare of horses used for PMU collection, much of the research conducted applies to all horses. Linwood has been certified by the Canadian Council on Animal Care (CCAC) which is a Canadian national organization similar to the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). The CCAC sets and maintains the standards for the care and use of animals in science in Canada. Since 2002, the CCAC has awarded Linwood a certificate of Good Animal Practice with each triennial assessment.

Through its research program, Linwood provides the quality assurance oversight for horses in the PMU industry. Research is used to validate and create standards

for horse care including the best way to manage equine ranches and control disease. After review by ERAB, research data obtained at Linwood is applied in various ways: a training resource for Pfizer Field Operations auditors, training and certification of veterinarians who conduct herd health reviews for the PMU ranching network, a source of current research and industry improvements for the *Recommended Code of Practice for The Care and Handling of Horses on PMU Ranches (2013)* and for the Pfizer rancher audit program, FARMS.

Linwood has a secondary function as a working PMU ranch which allows direct applicability of the research work and management to the PMU rancher network. Linwood has served to educate veterinarians and other professionals through continuing education programs such as dental flotation workshops; for ranchers and 4-H groups the emphasis is on the importance of high standards of care for all horses.

Under Pfizer leadership, Linwood Ranch continues to produce the research-based recommendations important to the continued improvement of the management of the horses producing PMU from which estrogens are extracted. The requirement for peer reviewed research is a basis for the American Association of Equine Practitioners' "Position on the Management of Mares Utilized in the Pregnant Mare Urine (PMU) Collection Industry" as revised by the AAEP board of directors in 2010. Linwood continues as a research and demonstration facility today. As an operating PMU ranch, Linwood is uniquely able to duplicate actual PMU management in a controlled research setting.

### **Linwood Research – Projects, Conclusions and On-Ranch Application**

The three main topics of horse management investigation have been watering, exercise/turnout and nutrition, although other areas such as foal growth, parasitology and vaccination have been investigated. Each research study is designed to answer questions of husbandry and welfare of PMU horses in terms of behavioral, clinical/physiological and farm management perspectives. This ensures that recommendations that arise from research are not only appropriate but that they can be implemented by ranchers or by other horse owners.

A fundamental component of studies at Linwood is horse behavior. A renowned equine behaviorist at the University of Pennsylvania examined 2,200 hours of videotapes of mares at Linwood Ranch. "All samples were free of abnormal behavior" and "As a population, these mares exhibited behavioral time budgets and daily activity patterns remarkably similar to those of pregnant mares in box stalls or at pasture" (McDonnell

et al., 1998). PMU mares had a very low incidence of stereotypical behavior (less than 5%) compared to stabled horses in the United Kingdom which had a 15 – 25% incidence of stereotypical or abnormal behavior (McGreevy et al., 1995).

Two aspects of studies at Linwood Equine Ranch ensure the validity of the research conclusions. These are:

- Review or collaboration of protocols by ERAB and LERACC (Linwood Equine Ranch Animal Care Committee) members and senior Pfizer management.
  - Use of statistically appropriate numbers of animals, e.g., water intake data were based on 18 to 42 animals per study.
- **Watering**  
A series of studies on water intake was initiated in 1995 to address the absence of data on the voluntary intake of water by stabled pregnant mares.

#### **Linwood Controlled Studies**

1. Continuous or manual, interval water delivery for PMU mares (40 mares; 1995-96)
2. Comparison of water intake, urine output and hydration status of PMU mares given continuous access or by two distinct intermittent timer water delivery systems ( 42 mares, 1996-97)
3. Design and testing of a stainless steel watering bowl with built-in float
4. Comparison of float water bowls – stainless steel Pfizer bowl, modified Pfizer bowl (Michie modification) and a commercial dairy bowl (18 mares; 1997-98)
5. Effect of high sodium and high sulfate content on water intake and nutrient digestibility of pregnant mares (16 mares; 2004-05)
6. The effect of frequency of water delivery on behavior of pregnant mares (42 mares, 2008-09)

#### **Field Studies**

1. Continuous water access – effect on PMU barn management (4 ranches, 1999-00)
2. Plant B Hybrid water bowl field trial (2000)
3. Identification of water quality on equine ranches (72 ranches, 2004-05)

## Conclusions

The results of studies on water delivery methods have been published (Freeman et al., 1999; McDonnell et al., 1999). It was concluded that intermittent water delivery methods were similar to continuous water access in providing appropriate amounts of water to maintain mare health and hydration. Intermittent watering was more hygienic than continuous access methods. Watering frequency, ranging from 4 to 12 times per day, did not affect hydration or health of the horses. Mare behavior was normal irrespective of watering system. All mare behavior was judged as clinically normal with no or low stereotypical behavior (McDonnell et al., 1998). These data were confirmed by Flannigan and Stookey (2002). Mares in PMU barns had behavioral time budgets and daily activity patterns similar to mares at pasture (McDonnell et al., 1999). Total daily rest by mares ranged from 11.1 to 11.8 hrs of which about 13% occurred in recumbent rest and 87% in standing rest (McDonnell et al., 1999).

Analyses of water obtained at equine ranches confirmed that 98% of water samples were within acceptable thresholds for total dissolved solids (TDS) and sulfate concentration (Cymbaluk, 2013). Horses on ranches with high normal water TDS and sulfate concentrations were clinically and physiologically normal. Subsequent short term testing of high sodium and sulfate water ingestion by pregnant mares showed that most horses quickly adapted to high concentrations of these elements although the drinking patterns were less predictable compared to water with low sodium and low sulfate concentrations.

### **Requirements and Current Practices on Pfizer Contracted Ranches**

All horses must have access to water at least 5 times daily provided in a stainless steel Pfizer engineer-designed or similar float design water bowl that has at least a 2 L reserve capacity. Every equine barn is equipped with an industrial water meter. Ranchers must log daily the total water consumption and the number of horses in the barn so that average individual water intakes can be determined. The Pfizer field auditor ensures that ranchers comply with the frequency of water delivery and examines water log book entries to ensure the adequacy of the individual mare water intake compared to the recommended water intake for the size of horse as stated in the *Code of Practice* (2013) which is based on NRC (2007) values. Field Auditors assess functionality and cleanliness of water bowls. The herd health review veterinarian similarly evaluates total daily water intake (gal/day), frequency of water delivery and duration of water delivery.

- **Turnout/Exercise**

A series of studies on turnout was initiated in 1996 and conducted through 2001, then refined using alternative technical equipment starting in 2011 through 2014, to address the absence of data on turnout programs for stabled pregnant mares. As it relates to pregnant mares, turnout (voluntary) is used instead of exercise (forced involuntary). The research studies conducted over that period to address this subject included the following titles:

### **Linwood Controlled Studies**

1. The comparison of daily, weekly and biweekly turnout on the clinical health, behavioral and biochemical status of pregnant mares (videotape, cortisol, clinical biochemistry especially serum enzymes for musculoskeletal assessment) (24 mares, 1996-97; 24 mares, 1997-98)
2. Comparison of daily, weekly and biweekly turnout on clinical health, behavior, serum biochemistry and the ontogeny and resolution of peripheral edema of the distal hind limb as measured by ultrasonography and physical measurements in pregnant and non-pregnant mares (26 mares, 1998-99)
3. Effect of diet and exercise on health and welfare of PMU mares (1999-00) (36 mares, high fiber vs low fiber diet and weekly vs biweekly turnout)
4. Validation of the IceTag<sup>®</sup> 3-axis accelerometer compared to videotaping for use in quantitation of pregnant mare lying, standing and movement behavior (12 mares, 2011-12)
5. Quantitation of the lying, standing and movement of pregnant mares in the barn using the IceTag<sup>®</sup> 3-axis accelerometer (12 mares, 2011-12)
6. Comparison of the lying, standing and movement of pregnant mares housed in box or tie-stalls and during weekly turnout (16 mares; 2012-13)
7. Comparison of the lying, standing and motion index of pregnant mares given different turnout frequencies during turnout and while in stalls (18 mares; 2013-14)

### **Field Studies**

1. Effect of weekly, biweekly or as-required turnout on mare health and barn management of two working PMU ranches (125 mares, 1999-2000)
2. Effect of biweekly or as-required turnout on mare health (infectious disease, colic, abortions, injuries) and barn management issues of 34 working PMU ranches (3100 mares, 2000-01)

### **Conclusions**

Results of the first turnout study were presented at the AAEP meeting in 1998 (Freeman et. al., 1998; McDonnell et al., 1998). Analyses of subsequent

studies showed that clinical and biochemical health of horses turned out daily, weekly or biweekly was normal. Behavior, which was evaluated using either sequential 24 hr. videotapes (over 4 years performed by Dr. Sue McDonnell) or 5-day IceTag<sup>®</sup> logs of stabled mares before and after exercise, confirmed no differences in behavior irrespective of turnout frequency. During the 1998-99 study, pregnant and non-pregnant mares were used in the turnout study. Dr. McDonnell observed that non-pregnant mares, whether turned out daily or biweekly, were significantly more active, more aggressive and less calm than pregnant mares under similar turnout conditions.

Based on videotape data and a 3-axis accelerometer, mares lie down a total of 1 – 2 hr. per day with a lying frequency of 2 – 6 times per day. Mares were recumbent longer ( $P < 0.05$ ) during late pregnancy (84.5 min) than during early pregnancy (32.7 min). Movement during a 3 hr. turnout did not differ statistically among mares turned out daily, weekly or biweekly.

Activity after turnout declined exponentially and plateaued after 20-30 minutes. Small bursts of activity occurred subsequently in a cyclical manner about every 30 minutes. The remaining time was spent standing or seeking food. During indoor stabling, non-pregnant mares were more active and more fidgety and aggressive than pregnant mares. Using GPS and IceTag<sup>®</sup> techniques, mares turned out weekly moved less often and moved less distance in late versus early pregnancy. Mares in early pregnancy moved for 59% of a 180 minute turnout and travelled 1.2 km. In late pregnancy, mares moved 36.6% of turnout time and travelled only 0.65 km.

Using a scoring system, stocking up (peripheral edema of the lower limb) in mares was observed primarily on entry into the barn, resolved quickly and was unrelated to turnout frequency (Freeman et al., 1998). The change in peripheral edema, which occurred only in the hind limbs, was quantitated through sequential, ultrasonographic images in 18 pregnant and 8 non-pregnant mares over a collection season. This analysis confirmed that peripheral edema, when and if it occurred, was associated with pre-existing or self-inflicted clinical conditions and was always peri-tendinous. Pre-existing conditions that caused peripheral edema included fibrosis secondary to healed lacerations or in response to splint reactions and acute self-inflicted wounds (hematomas) associated with kicking. Ventral edema increased with advancing pregnancy in some but not all mares, and was largely unresponsive to turnout. Ventral edema was not correlated with peripheral limb edema. Mares with large udders and varicose caudal epigastric veins (mammary) were prone to ventral edema.

### **Requirements and Current Practices on Pfizer Contracted Ranches**

Required turnout frequency depends on the individual horse. Ranchers are instructed to assess the clinical and behavioral well-being of each horse and to turn that individual out accordingly. Individual turnout supersedes the contract requirement of a minimum biweekly turnout of mares for at least one hour in a paddock providing at least 1000 sq. ft. space per mare. Turnout paddocks must be safe and protected from wind. Turnout for each mare is logged in a Pfizer logbook. Entries of each mare's turnout (exercise) is reviewed monthly by the Pfizer field audit team during the collection season and all turnout log books are reviewed by the Field Operations unit at the end of the season. Veterinarians evaluate the turnout program – frequency, adequacy of turnout facility – and record comments on Herd Health Reviews.

- **Nutrition**

Nutritional studies reviewed the impact of diet quality and composition in the context of physiology, behavior and management. The following studies have been conducted:

1. Effect of feeding early and late cut hay on the nutritional balance, water intake, urine output, health and barn management of pregnant mares (20 mares, 1997-98; 62 mares, 2009-10)
2. The effect of the amount of dietary salt (low normal, normal and high normal) on peripheral limb edema and dietary utilization of sodium by pregnant mares (30 mares, 1998-99)
3. Effect of forage-only diets in the management of PMU mares:
  - a. Behavior and physiology of mares fed hay-only diets or soybean meal-supplemented diets compared to a control diet of hay and oats (45 mares, 2000-01)
  - b. Behavior and physiology of mares fed oats hay (green feed) diets compared to a traditional hay and oats diet. (126 mares, 2000-01)
4. Effect of forage-only, soybean meal and canola meal protein-supplemented diets compared to a traditional hay and oats diet in the management of PMU mares (40 mares; 2001-02)
5. Dietary fiber and PMU mare management (56 mares, 2002-03)
6. Effects of lysine and threonine (amino acid) supplementation of pregnant mare diets (60 mares, 2005-06)
7. Comparison of morphometrics and clinical chemistry of weanling foals fed normal or fat-supplemented concentrate (2007-08)



## Conclusions

Diets providing protein in excess of National Research Council (2007) requirements for pregnant mares increased urine output without changes in water intake. Feeding high quality alfalfa hay doubled urine output by mares, compared with those fed timothy hay, but fractionally increased water intake. Feeding high fiber hay, contrary to popular belief, resulted in a lower incidence of colic than in mares fed high quality forage, when fed with a good water supply. Behavior of mares did not differ when fed an all-forage diet versus a forage-grain (grain mix) diet. Manitoba and Saskatchewan forages are low in trace minerals but provide an adequate amount of lysine and threonine if fed in combination with appropriate grain mixes. Salt fed at low normal, normal and high normal amounts had a minor impact on urine output, but influenced apparent sodium digestibility.

### **Requirements and Current Practices on Pfizer Contracted Ranches**

Diets fed to PMU mares must meet the minimum nutrient requirements for pregnant mares (NRC, 2007). Feeds, especially hays, must be tested prior to being fed to mares used in PMU collection. Ration formulation is recommended but not required. The nutrient analysis of feeds and adequacy of diets used on ranches are reviewed by the company veterinarian and by private veterinary practitioners that conduct Herd Health Reviews. Contract requirements necessitate that ranchers attest that no feed supplements contain animal by-products. Feed type and amounts fed to mares and other horses are recorded in the Pfizer Field Operations monthly audits and on each Herd Health Review. Mineral, vitamin and salt supplementation is required and amounts provided are recorded during audits and herd health reviews.

- **Alternative Collection Methods**

1. Evaluation of a commercially available equine diaper as an alternative to the suspension device harness for urine collection (4 mares, 1998)
2. Evaluation of the PMU suspension harness (boot on versus boot off) on mare behavior (38 mares; 2001-02; 10 mares, 2012-13)
3. Modifications to the PMU suspension harness support system (demonstration) (6 mares, 2005-06)

## Conclusions

An alternative method using an equine diaper was tested for use in PMU collection. The equine diaper (as tested at Linwood) was a plastic harness with many contact points (chest, back, girth, and perineum). The unit collected all excreta – feces and urine – which greatly increased the weight of the device creating rub marks at contact points. Cleaning the unit took 45 minutes.

Accumulated fluid and the plastic straps froze in outdoor winter temperatures. Mares tolerated the unit poorly.

Based on two studies which evaluated mare behavior by videotape or IceTag<sup>®</sup> accelerometer, the current suspension harness does not interfere in lying or movement behavior of mares compared to the same mares when unharnessed. Evaluations of the harness support system concluded that the suspension system is adjustable in various ways so that it can match the individual conformation of the horse.

**Requirements and Current Practices on Pfizer Contracted Ranches**

Ranchers must use the collection methods as described in the *Recommended Code of Practice for Horses on PMU Ranches (2013)*. Any modification to the collection system must be approved by the PMU Code of Practice Committee.

• **Husbandry and Management**

1. Demonstrational testing of dairy mattresses (standard dairy, pasture mat ) for use in equine stalls and height of rubber on stall partitions(4 mares, 1996)
2. Time distribution of PMU horses on pasture (20 horses, 1996)
3. Demonstrational testing of a hook-line and sinker tethering method (3 mares, 1996-97)
4. Evaluation of bedding for mares under standard and PMU conditions (rubber mats, wheat straw or flax shives) (18 mares; 2001-02)
5. Acclimation to PMU stable (53 mares; 2000-01)
6. Mare morphometrics and stall width (16 mares, 2004-05)
7. Longitudinal assessment of bio burden and endotoxin loads: air quality and cleaning frequency and identification of airborne microbiota in a PMU barn (1 barn, 2006-07)
8. Comparison of morphometrics and hoof growth of foals fed normal or fat-supplemented rations (24 weaned foals, 2007-08)
9. Measurements of body weights of mares in late pregnancy – rancher network (21 ranches, 2009)

**Conclusions**

The conventional dairy mat is tolerated well by horses and is sufficiently durable to withstand the activity of horses. Slipping on hard dairy mats is not problematic because urine is collected and straw bedding on top of mats absorbed moisture from feces. Pasture mats did not tolerate the weight and

activity of horses (pawing and forelimb activity) and were destroyed or misshapen by horses within a short period of time.

The hook-line and sinker tethering was superior to traditional fixed lead shanks. The system has been used successfully for 18 years. Safety is the principal feature in using the hook-line-sinker method.

Wheat (and barley) straw is the most cost effective bedding in Manitoba. Flax shaves adhered to mares' hair coat and was a mild irritant. Non-bedded mares reclined less often and for shorter periods of time. After bedding was provided to non-bedded mares, recumbence increased in frequency and duration.

Air quality in the barn did not differ in mold/fungal and bacterial contamination in November compared to January. The main fungi in barn air were *Cladosporium* and *Alternaria*. Mold/fungal count did not differ before and after bedding the stalls. Yet, total bacterial colonies (cfu/m<sup>3</sup>) doubled after bedding (from 4980 cfu/m<sup>3</sup> before to 9440 cfu/m<sup>3</sup> after bedding). Bacteria identified on ribotyping included various plant bacteria and skin microflora such as *Pantoea spp*, *Staphylococcus xylosus* and *sciuri*, *Micrococcus spp*. These numbers are typical of equine barns.

Mares acclimate to the barn quickly. Daily time budgets and activities are achieved by day 3 after barn entry and normal recumbence patterns by day 19 and are unrelated to age or PMU barn experience. Behavior of Quarter Horse mares of various wither heights and body weights did not differ according to stall size. Body weights of horses on 24 equine ranches were taken and confirmed compliance with the PMU Code of Practice with respect to housing.

**Requirements and Current Practices on Pfizer Contracted Ranches**

Straw bedding (wheat, barley, but oats less so) at a depth of 4 to 6 inches is recommended. Field auditors and independent private practitioners record the adequacy of bedding in stalls. Stall sizes must meet the specified dimensions for the mare's weight into her last trimester of pregnancy as listed in the *Recommended Code of Practice for the Care and Handling of Horses on PMU Ranches (2013)*.

PMU barns are mechanically ventilated which reduces fungal and bacterial growth. PMU barns must be cleaned daily and bedded with fresh, clean straw. Water bowls and mangers must be kept clean; they are monitored and recorded monthly for cleanliness by the Field Audit team.

- **Specific Veterinary Testing**

The following studies on routine herd health have been performed.

1. A randomized controlled double-blind trial to compare the effect of prophylactic dental flotation on weight gain, body score and fecal particle size of PMU mares fed four different diets (56 mares, 2001-02)
2. An evaluation of strangles prevention in foals at various ages using an intranasal strangles vaccination (66 mares, 40 foals, 2002)
3. Effect of using a conditional West Nile Virus vaccine given to PMU mares (40 mares, 2003)
4. Comparison of pregnancy testing by manual versus laboratory methods (56 mares, 2004-05)
5. Bacterial populations in free-flow urine of pregnant mares (39 mares, 2005-06)
6. Penicillin clearance in urine from pregnant, healthy mares (10 mares, 2006-07)
7. The epidemiology of equine herpes virus –1 (EHV-1) and –4 (EHV-4) in pregnant mares and their offspring from birth through weaning (50 horses, 2007-08)
8. Use of the biological microchip to measure body temperatures in horses (35 mares, 2007-08)
9. Safety testing of a commercial encephalomyelitis-influenza-West Nile virus vaccine, Eastern and Western killed virus vaccine, and tetanus toxoid in foals under field conditions (89 foals, 2008)
10. Evaluation of internal parasites by fecal analysis and estimation of vermifuge (ivermectin, fenbendazole) resistance through FECRT on an equine ranch (52 mature horses, 2010-11)
11. Placental weights of foaling mares after a PMU collection season (43 mares, 2010-11)

**Conclusions:**

Dental flotation effects on feed digestibility were examined in 40 mares allocated at random to 4 different diets (all hay or hay-grain based). Neither dental flotation nor molar occlusal angles between 6 and 19 degrees were found to influence body weight gain, feed digestibility or fecal particle size (Carmalt et al., 2004). No association was found between age and molar occlusal angle (Carmalt et al., 2005).

Intranasal strangles vaccine was administered to twelve mares 6 weeks pre-foaling and withheld from fifty-four (54) controls. No to low antibody titers to *Streptococcus equi* were produced in response to intranasal vaccine. At

birth and post-suckling, foals born to vaccinated mares had no antibody to *Strep equi* indicating no trans-placental or colostral transfer of antibody.

Foals from the 12 vaccinated pre-foaling mares and from 28 of the 54 control mares were then given 2 cc vaccine intranasally at ages ranging from 7 to 41 days of age (median = 18 days of age). Foals from the original controls were unvaccinated and served as the study controls. Three vaccinated foals (7, 24 and 41 days of age) developed clinical signs of strangles. The youngest foal developed a severe guttural pouch empyema. Submaxillary abscesses were swabbed and confirmed to be *Streptococcus equi* in two foals. The laboratory could not distinguish if the *Streptococcus* was a wild or vaccine strain. The third foal was confirmed to be infected with a *Streptococcus zooepidemicus*.

No remarkable findings were observed with use of the West Nile Virus vaccine in the second trimester of pregnancy or with the vaccination of foals with 5-way vaccine. All horses were normal post-vaccination.

Pregnancy detection by rectal palpation methods showed high individual accuracy of veterinarians and high conception rates of mares (average 90%) in the industry. Rectal palpation was an excellent screening method for pregnancy confirmation.

Urinary bacterial populations of free-flow urine were normal. Placental area and umbilical cord dimensions of post-foaling PMU mares were normal.

Penicillin clearance in urine by 10 late pregnant mares given 21,000 IU/kg twice daily for 5 days averaged 4.4 days. The average peak of urinary penicillin was 10,000 µg/kg BW about 48 hr. after the first injection. The calculated half-life for penicillin residues in urine varied widely for mares (average:  $15.2 \pm 8.4$  hr.; range 3.7 – 31.3 hr.). Washout of penicillin also varied widely (average  $4.4 \pm 2.4$  days; range 1.1 – 9.1 days). A suggested withdrawal period from the last injection of penicillin to encompass all mares is at least 9 days.

A typical pattern of EHV-1 and EHV-4 titre was observed in 45 newborn and weanling foals born to EHV-1 vaccinated PMU mares. About 50% of mares had a protective titer to EHV-1 following a third vaccination with a killed virus vaccine which persisted for 6 months. Though unvaccinated against EHV-4, about 93% of mares were seropositive in the 8-month test period. No foals were seropositive for EHV-1 and EHV-4 pre-suckling. A day post-suckling, 42% of foals were seropositive to EHV-1 and 96% of foals were seropositive to EHV-4. Seroprevalence waned for both EHV-4 (73%

seroprevalence post-weaning) and EHV-1 (13% seroprevalence post-weaning) up to weaning. Two foals had no EHV-1 titer until weaned when titers increased. This suggested an active EHV-1 infection.

A microchip that was commercially developed to monitor body temperatures of horses quickly and easily was tested. The microchip was implanted in the left nuchal ligament of 37 pregnant light, crossbred and draft horse mares. Temperature readings from the microchip were compared to rectal body temperatures taken for 21 days with a digital thermometer. The average rectal temperature was  $37.7 \pm 0.22$  C compared to  $36.0 \pm 1.42$  C for the microchip. There was poor correlation between digital thermometer and microchip temperature ( $r=0.198$ ).

The fecal parasite load of 52 mares, 7 stallions and 58 foals was examined. A fecal egg count reduction test (FECRT) was conducted in mares to determine if vermifuge resistance was present. In mature horses, the prevalent helminth species were strongyles and very occasionally *Oxyuris* (pinworms). Post-weaning fecal egg counts (FEC) of foals that had been dewormed with pyrantel in August were low and species were typed as mainly strongyles, with a few ascarids and pinworms. Average FEC was  $95 \pm 41$  epg for mares. Based on a 95% upper confidence limit the baseline FEC for the Linwood herd was about 150 epg. Eight of 52 mares (15.4%) consistently exceeded this amount irrespective of which of the 2 dewormers was used. Using the recommended equine dosage rate, the FECRT for ivermectin was 99% indicating no resistance in this herd. The FECRT for fenbendazole was 90% which might suggest resistance. However, fenbendazole was only used for two years in this herd and only once per year. This would suggest other causes for the low FECRT such as an inadequate dosage either through poor dosing technique or low dosage rates as per manufacturer.

### **Requirements and Current Practices on Pfizer Contracted Ranches**

Each mare intended to be used for PMU collection must be confirmed pregnant by a licensed veterinarian. Mares must be identified by a unique name or brand and entered into a Pfizer logbook. Documentation of the pregnancy test (logbook) must be signed by the veterinarian and submitted to Pfizer before urine collection.

Vaccination to protect against equine influenza and West Nile virus is mandatory by contract. Each rancher must sign a certificate verifying the veterinary clinic where the vaccine was purchased, date the vaccine was administered, the vaccine name, the vaccine batch and the purchase invoice number for the vaccine. Vaccination to protect against tetanus and Western equine encephalomyelitis is required by the PMU *Code of Practice*.

Vaccination to protect against equine herpes virus 1 and 4 is determined by the attending veterinarian for each herd.

Dental flotation is recommended on an as-needed basis. Veterinarians record if any specific horse requires dental flotation in the Herd Health Review. Two dental flotation short courses were given to herd health veterinarians at Linwood by acknowledged western Canadian equine dentists. No limitations are imposed on veterinarians in using any pharmaceutical product required to treat any horse on equine ranches. However, urine must be withheld from PMU collection from any medicated horse until drug clearance has occurred (based on the Canadian Pari-Mutuel Agency Schedule of Drugs).

Based on the fecal egg count for horses at Linwood Equine Ranch and by veterinarians at other equine ranches, the recommended minimum deworming schedule for adult horses is twice per year. Compliance with this deworming schedule occurs on 100% of equine ranches. The recommended frequency for deworming of foals and young horses is left to the discretion of the attending veterinarian for each ranch.

- **Equine Arteritis Virus Testing of Stallions**

**Requirements and Current Practices on Pfizer Contracted Ranches**

In July 2005, mandatory equine arteritis virus (EAV) testing of stallions was required for ranchers holding contracts with Pfizer. Testing of 772 resident stallions in the PMU industry was completed in September 2005. Since then, any new stallion entry into the PMU resident herd must be tested before use in breeding of mares used in PMU collection. Serum samples are collected by practicing veterinarians and submitted to the APHIS lab at Cornell University (Ithaca, New York). Seropositive stallions can only be used for breeding purposes after semen testing by the Cornell University lab or the EAV laboratory at the University of Kentucky. Vaccinated, seropositive horses must be semen tested unless detailed proof of vaccine serial number, date of administration and administering veterinarian are provided. Confirmation of the effectiveness of EAV testing program was made by urine testing of a representative sample of pregnant mares on all ranches for EAV remnants by PCR methods at an outsourced laboratory. Over the 4-year study testing period, all urine samples were negative for EAV remnants substantiating the effectiveness of EAV testing program. Testing is paid for by Pfizer.



## **NORTH AMERICAN EQUINE RANCHING INFORMATION COUNCIL, INC.**

Established in February 1995, the North American Equine Ranching Information Council, Inc. (NAERIC) is a non-profit association of equine ranchers engaged in horse production and management of the pregnant mares used in PMU equine ranching. NAERIC serves its members, the horse industry and general public as an agribusiness resource by providing the latest information and research on ranch management, equine care, breeding practices and innovative marketing programs. NAERIC responds to inquiries by the public regarding welfare of mares used in PMU collection to ensure accurate information. The council is dedicated to ensuring the NAERIC brand represents overall quality. NAERIC supports and promotes the partnership between agriculture and women's health care. Detailed information can be found at [www.naeric.org](http://www.naeric.org).

### **NAERIC Marketing Programs**

NAERIC has created innovative marketing programs that assist placement of the resulting foals with individual buyers. NAERIC initiatives support the management, care and placement of equine ranching industry horses into productive markets throughout the United States and Canada. Programs cover light horse breeds, crossbreds and heavy horse breeds thus ensuring that all NAERIC member ranchers have access to promotional programs that assist in selling their horses.

NAERIC has established several initiatives that help ensure the continued breeding of quality horses. The quality of the resulting horses has been said to be "the best kept secret in North America." Some examples are identified below.

- **NAERIC *Advantage*<sup>®</sup>**  
The NAERIC *Advantage*<sup>®</sup> is an incentive program for horses bred on NAERIC member ranches. More than 51,000 NAERIC-registered horses are eligible to earn NAERIC *Advantage*<sup>®</sup> rewards when competing successfully at approved events throughout North America. Since 1998, more than \$3 million in NAERIC *Advantage*<sup>®</sup> payouts have been distributed to owners of NAERIC horses. The NAERIC *Advantage*<sup>®</sup> encourages the purchase of horses from NAERIC ranchers and the promotion of these horses as successful show horses.
- **CanAm Sport Horses<sup>®</sup> Breeding Program**  
CanAm Sport Horses<sup>®</sup>, blending quality with affordable prices, are produced by crossing predominantly draft-cross mares with Thoroughbred stallions that meet the needs of sport horse enthusiasts from the show ring to the hunt field, including recreational riding. This program promotes these offspring into sport horse markets.

- **NAERIC Draft Horse Classic Sale and Futurity**

Breeders of quality draft horses are members of the NAERIC Draft Horse Classic Committee and participate in this unique program which began in 2001, and was held annually at the Canadian Western Agribition in Regina, Saskatchewan. In 2012 the event was moved to the Royal Manitoba Winter Fair in Brandon, Manitoba. Some of the finest Percheron, Clydesdale and Belgian draft horses in western Canada have been nominated to the NAERIC Draft Horse Classic Sales.

This program entitles breeders to consign and sell two registered or non-registered yearlings at auction each spring. The horses sold through the sale return as three-year-olds to compete for a significant purse at the futurity designed to demonstrate their quality, conformation and performance. The 2014 NAERIC Draft Horse Futurity featured a total purse of \$57,780.00 – the richest purse for three-year-old draft horses competing in North America.

- **NAERIC Versatility Ranch Horse Stake**

In 2008, the NAERIC Versatility Ranch Horse Stake was launched. Goals were to: 1) increase awareness of the NAERIC-bred ranch horse as a market opportunity; and 2) continue the development of these horses, and create a value-added opportunity for a segment of equine enthusiasts interested in owning a NAERIC-registered horse.

This annual event features a NAERIC stake class open to three-year-old registered NAERIC, American Quarter Horses, Paints and Appaloosas sired by NAERIC-member owned, nominated stallions. NAERIC-registered 2011 foals sired by nominated stallions will be eligible to compete for the 2014 NAERIC stake purses which are estimated to be \$4,725.00.

- **NAERIC Barrels of CA\$H Sale and Futurity**

Also launched in 2008, the NAERIC Barrels of Cash Sale and Futurity marketing program was developed by NAERIC-member equine ranchers. The sale weanlings are registered with both NAERIC and their respective breed associations. The highly successful NAERIC Barrels of Cash Prospect Sale was held in the Keystone Centre's Amphitheatre in Brandon, Manitoba, in October 2008. The concept was to consign weanlings that would return as five-year-olds to compete in a barrel horse futurity. Only weanlings purchased through these annual Barrels of Cash Prospect Sales are eligible to compete at future NAERIC Barrels of Cash Futurity events. This inaugural sale, held in conjunction with the Wheat City Stampede, attracted a large crowd. Bidders were registered from Alberta, Manitoba and Saskatchewan. Buyers purchased weanlings consigned by NAERIC-member equine ranchers. The sale average on 37 head was \$910, with the top five weanlings averaging \$1,855, and the top ten averaging \$1,580.

The inaugural running of the \$9,000 NAERIC BARRELS OF CASH Futurity took place in 2013 during the Wheat City Stampede at the Keystone Centre, Brandon, MB. The organizers were ecstatic to have 20 paid entries for the race from the original 37 foals that sold five years earlier. The winner took home \$3,600; second place was worth \$2,160; third place paid \$1,440. The futurity was run in a 2D format with additional payouts going to those contestants. Thirty-eight prospects for the 2018 futurity sold later the same day for an average of \$1,030.

- **Young Horse Development Program**

The Young Horse Development Program was launched in 1998 from a partnership forged between Manitoba 4-H and the Manitoba Equine Ranching Association (MERA), a member of NAERIC. This program has since expanded to Saskatchewan, where it includes participation of other youth groups.

The objective of the program is for 4-H members to raise and train the horse they purchase from NAERIC-member ranchers, and present it first as a yearling in hand, and then as a two-year-old green broke prospect the second year. It involves a two-year commitment, and gives 4-H members the opportunity to learn not only training techniques and methods, but valuable life skills about taking responsibility, setting goals and meeting deadlines, problem solving, confidence building, establishing work ethic, seeking out knowledge and information, making commitments, and exercising patience.

- **Youth Extravaganza**

NAERIC partnered with the Manitoba 4-H Program from 2002 – 2012 to host the NAERIC Youth Extravaganza which drew more than 400 youths and leaders from Manitoba, Saskatchewan, northwestern Ontario and North Dakota to attend this horsemanship skills clinic. The clinic, free to all youths and their leaders, was held each October during the Wheat City Stampede – a weekend of equine activities and attractions in Brandon, Manitoba. This program was developed to ensure young people would gain the skills necessary to become informed, responsible and knowledgeable horsemen of the future.

- ***Shop For a Look You Like***

In 2009, NAERIC launched the popular “Shop for a Look You Like,” sales approach. The concept is based upon the web site feature of successful commercial retailers that gives shoppers the opportunity to view products and request the same from the retailer. This feature administered via the NAERIC web site, [www.naeric.org](http://www.naeric.org), gives on-line visitors the opportunity to view multiple images of various breeds, colors, coat patterns etc., and choose the types they seek. The shopper then chooses the preferred sex, requests specific genetic lines and eventual size, and submits the request to the NAERIC office. NAERIC then distributes each request to the entire rancher network in an effort to fill the order of the potential buyer. Individual ranchers can then contact the buyer directly and send photographs, videos and other information specific to the horse(s) the rancher believes would meet the requests of the potential purchaser. This feature has proved to be very successful in matching equine ranchers with potential buyers.

- **Database Since 1998**

Since 1998, NAERIC has maintained an extensive database of ranchers, horses, private-treaty buyers, registration details, NAERIC Advantage events and payouts as well as horses eligible for the various NAERIC programs. Through a “Members Only” feature, ranchers are able to register their horses for NAERIC programs on-line. The database records information for registered horses. In addition, non-pedigreed horses are tracked via a unique 15 digit ISO 11784 compliant microchip number that can be read by any ISO compliant reader. The combination of registration and microchip information in the database allows NAERIC the opportunity to track horses back to their original breeders should questions arise as to the origin of any horse.

### **NAERIC’s Educational Role**

NAERIC has conducted continuing education opportunities for its ranchers in addition to supporting third party educational opportunities such as those of the Alberta Horse Breeders’ & Owners Conference, Saskatchewan Horse Federation, Alberta Farm Animal Care, Farm Animal Care Saskatchewan Disaster Training, and the Curt Pate Horsemanship Clinic.

NAERIC has provided financial support for consultant services specific to financial planning via the Canadian Farm Business Advisory Services. Services include farm business assessment, business planning and farm financial assessment.

Another resource is the *Digest & Reference for Effective and Efficient Marketing* manual, first produced in 2005. This is a series of interactive programs and reference materials related to NAERIC horse marketing, advertising and promotion that has been updated to meet market requirements and ensure the placement of horses in productive markets.

In addition, NAERIC has hosted, at no cost to ranchers, educational marketing seminars to ensure there is basic knowledge and understanding of concepts on which to build successful marketing campaigns based on increased awareness about equine markets. These seminars allowed NAERIC to accurately assess the ranchers' marketing needs, their current levels of marketing activity and offer methodologies to provide meaningful assistance.

### **Equine Industry Research Support**

For decades, equine ranchers, through a network-wide check-off program, have supported research at universities including the Western College of Veterinary Medicine (University of Saskatchewan), University of Minnesota, Oklahoma State University, North Dakota State University, and the Alberta Ministry of Agriculture. Research projects have included reproduction, nutrition, behavior and disease related topics. These research efforts have yielded recommendations for not only the equine ranching industry, but for the horse industry at large.

NAERIC is a financial supporter of the Equine Health Research Fund at the Western College of Veterinary Medicine (WCVM), whose research plays a key role in enhancing veterinary training and improving equine health. NAERIC's contributions help support research projects of value to the equine ranchers' network and the horse industry at large. In addition to its research activities, WCVM is closely involved in educational initiatives that will have a long-term impact on the role of the veterinary college and the veterinary profession on public health.

NAERIC's annual financial support is used by the WCVM to help: 1) make world-class equine research projects possible; 2) provide funding for fellowships and awards for graduate and undergraduate students pursuing their interest in equine veterinary medicine; 3) assist equine specialists educate other professionals, horse owners and equine associations; 4) advance public education through *Horse Health Lines*, the WCVM equine information and education newsletter.

### **The Lavin Cup, the Equine Welfare Award of the AAEP**

The purpose of this award is to recognize a non-veterinary organization or individual that has demonstrated exceptional compassion or developed and enforced rules and guidelines for the welfare of horses. The American Association of Equine Practitioners honored NAERIC-member family-ranchers dedicated to improving equine welfare through research, education, and innovative marketing with the 2009 Lavin Cup. “Our approach from inception has been to rely on science-based horse management, continuous improvements and working with equine veterinarians for education, recommendations and oversight that ensure the health and welfare of the horses we manage” said the 2009 NAERIC president. “Our family-ranchers are proud to be horse breeders who contribute to women’s health care and are especially appreciative of the recognition by the American Association of Equine Practitioners for our equine welfare initiatives.”

### **Equine Placement Fund**

In connection with the downsizing of the PMU network due to decreases in demand for estrogen therapies, Pfizer provided funding commencing in October 2003 through December 2006 to the former PMU ranchers to cover the feed and herd health needs of the horses no longer required for collection. In addition, Pfizer established an Equine Placement Fund (EPF) in 2003 to assist ranchers in placing their horses into productive markets. EPF is assisted in this effort by an equine placement advisory board that includes veterinarians and equine specialists. Due to the great success of the program, Pfizer added additional funding to be used to continue placement activities for remaining network ranchers. To date, total funding has been over \$12 million dollars with additional commitment of funds through 2014.

NAERIC plays an instrumental role in the EPF process, including: 1) identifying potential sales opportunities; 2) researching private treaty buyers, public auctions, specific breed sales, embryo transplant recipient buyers, etc., and validating them as legitimate buyers and markets; 3) validating reimbursement requests for expenses associated with transportation, international veterinary health paperwork, border fees, etc.; 4) processing requests for reimbursement of other promotional opportunities associated with EPF, such as breed incentives, registration incentives, advertising assistance and technology improvements that support horse sales.

NAERIC has managed the EPF since its inception. The fund has been instrumental in moving more than 30,000 horses into productive markets in 48 states and every Canadian province.

**NAERIC Marketing Assistance Program**

A new generation program which assists ranchers with placing horses in productive markets was modeled after the Equine Placement Fund and fully implemented in 2014. The NAERIC Marketing Assistance Program (MAP) focuses on more traditional marketing of foals to horse enthusiasts with a greater interest in show ring and competition venues. This logical extension of the EPF utilizes an advisory board much the same as the EPF, but much more focused on the marketing of horses.

NAERIC remains committed to these breeder incentives, stallion improvement and consignor/seller incentive programs through their continuing administration of MAP on behalf of the ranching network.

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## REFERENCES

1. Carmalt, J.L., H.G.G. Townsend, E.D. Janzen and N.F. Cymbaluk, 2004. Effect of dental floating on weight gain, body condition score, feed digestibility and fecal particle size in pregnant mares. *J. Amer. Vet Med Assoc.* 225: 1889-1893.
2. Carmalt, J.L., N.F. Cymbaluk, and H.G.G. Townsend. 2005. Effect of premolar and molar occlusal angle on feed digestibility, water balance and feed particle size in horses. *J. Amer. Vet Med Assoc.* 227: 110-113.
3. *Code of Practice for the Care and Handling of Equines.* 2013. National Farm Animal Care Council. Equine Canada. Ottawa, Canada.
4. Cymbaluk, N.F. 2013. Water. Chapter 4 in *Equine Applied and Clinical Nutrition. Health, Welfare and Performance ed. R.J. Geor, P.A. Harris, and M. Coenen. Saunders, Elsevier. Toronto. Pp 80-95.*
5. Flannigan, G. and J.M. Stookey. 2002. Day-time time budgets of pregnant mares housed in tie-stalls: a comparison of draft versus light mares. *Appl. Anim. Behav. Sci.* 78: 125-143.
6. Freeman, D.A., N.F. Cymbaluk, B. Kyle, H.C. Schott, K. Hinchcliff, and S.M. McDonnell and B. Kyle. 1998. Health and welfare of stabled PMU mares under varied water and turnout schedules: 1. Physiology. *Proc. Annu. AAEP* 44: 19-20.
7. Freeman, D.A., N.F. Cymbaluk, H.C. Schott, K. Hinchcliff, S.M. McDonnell and B. Kyle. 1999. Clinical, biochemical, and hygiene assessment of stabled horses provided continuous or intermittent access to drinking water. *Amer. J. Vet. Res.* 60: 1445-1450.
8. King, A.B., N.T. Messer and C.A. Roberts, 1997. *Equine Veterinarians' Consensus Report on the Care of Horses on PMU Ranches.* A report submitted to Wyeth Pharmaceuticals.
9. McDonnell, S.M., D.A. Freeman, N.F.Cymbaluk, B. Kyle, H.C.Schott, and K. Hinchclif. 1998. Health and welfare of stabled PMU mares under various watering methods and turnout schedules: 2. Behavior. *Proc. Annu. AAEP* 44: 21-22.
10. McDonnell, S.M., D.A. Freeman, N.F.Cymbaluk, H.C.Schott, K. Hinchcliff and B. Kyle. 1999. Behavior of stabled horses provided continuous or intermittent access to drinking water. *Amer. J. Vet. Res.* 60: 1454-1456.
11. McGreevy, P.D., P.J. Cripps, N.P. French, L.E. Green and C.J. Nicol 1995: Management factors associated with stereotypic and redirected behavior in the thoroughbred horse. *Equine Vet. J.* 27: 89-91.
12. Messer, N.T. 2011. PMU Ranching and Equine Welfare. Chapter 16 in *Equine Welfare* ed. C.W. McIlwraith and B.E. Rollin. Blackwell Publishing Ltd. Pp 318-331
13. Nutrient Requirements of Horses. 2007. 6<sup>th</sup> Revised Edition. National Research Council of the National Academies. Washington, D.C.

14. National Animal Health Monitoring System (NAHMS) 1998 and 2005 Equine Study. Animal and Plant Health Inspection Service. Veterinary Services. Centers for Epidemiology and Animal Health.
15. *Recommended Code of Practice for the Care and Handling of Horses on PMU Ranches*. 2013. 6<sup>th</sup> revision. PMU Study Committee. Brandon, Manitoba.
16. Statistics Canada. 2007. Weather conditions in capital and major cities. <http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/phys08b-eng.htm>.
17. Stefanick, M.L. 2005. Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. *Amer. J. Med* 118: 64S – 73S.