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Food and Drug Administration  
5630 Fishers Lane, Room 1061  
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Response to Docket No. 2002N-0273, Proposed Rule Substances Prohibited From Use in Animal Food or Feed

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**Executive Summary**

***APC, Inc. agrees with the conclusion of the FDA that there is no scientific evidence to suggest that BSE infectivity is present in bovine blood. Banning the use of bovine blood or blood fractions in ruminant rations will not reduce the risk of exposure of humans or animals to BSE infectivity. Animal health will be compromised if the use of bovine blood or blood proteins in ruminant feeds is restricted.***

APC, Inc. is a member of the North American Spray Dried Blood and Plasma Producers Association (NASDBPP) (see **Appendix A**). The NASDBPP is a group of companies located in North America involved in the production and development of spray dried blood and plasma products. These companies organized a working group within the American Feed Industry Association (AFIA) with the purpose of developing Manufacturing Standards to insure that the safety of blood derived proteins is preserved. In addition, it is the intention of NASDBPP to insure that data supporting the safe nature of these proteins is communicated to industry and government officials. The NASDBPP is committed to producing safe, high quality blood products for use as an ingredient in feeds for commercial livestock and companion animals.

BSE infectivity has never been detected in blood or any component of bovine blood. There is no epidemiological evidence that bovine blood or blood component carries BSE infectivity. Spray dried blood and plasma products are consumed orally, which is the least efficient method of transmission (100,000 times less efficient compared to intracranial injection). The NASDBPP developed Manufacturing Standards to insure that our blood products do not become contaminated with high-risk tissues. The Manufacturing Standards have been reviewed by internationally recognized BSE experts. Finally, the NASDBPP have agreed to and completed annual third party inspections to certify compliance to these Manufacturing Standards.

It is critically important that regulatory policy developed to prevent BSE from becoming established in the US cattle population is grounded on sound science. The NASDBPP support APHIS, FSIS and FDA in their efforts to develop policies to mitigate the risk of BSE. The NASDBPP appreciate the opportunity to comment on the questions and issues raised in the Proposed Rule, Docket No. 2002N-0273, Proposed Rule Substances Prohibited From Use in Animal Food or Feed. We will restrict our comments to the request for further comment and scientific information regarding the need to prohibit the use of blood and blood products in ruminant feed.

## ***APC, INC. COMMENTS***

***There is no scientific evidence to show that the use of bovine blood or blood products in feed pose a risk of BSE transmission in cattle and other ruminants.***

### **A. BSE infectivity has never been detected in bovine blood.**

Bovine blood has never been implicated in bovine-to-bovine transmission of either natural or experimental BSE (European Commission Scientific Steering Committee (SSC), April 2000; SSC, October 2000). Despite intensive research trials and detailed epidemiological evidence, no BSE infectivity has been detected in bovine blood in either natural or experimental cases (Bradley, 1993, 1999, 2000; Fraser et al., 1992; Kimberlin and Wilesmith, 1994; Middleton and Barlow, 1993; Moon, 1996).

BSE infectivity has not been detected in the buffy coat, spleen or lymph nodes from naturally or experimentally infected cattle when bioassayed in susceptible mice or directly in calves (Wells, et al., 1994; 1998). In an experiment initiated in 1996, buffy coat from a BSE infected cow (the cow was experimentally infected and the blood cells were collected 32 months post exposure) was injected intracerebrally into recipient calves. To date (over 7 years post exposure) the recipient calves have not developed BSE (Dr. Ray Bradley, 2004, personal communication).

Following the discovery of BSE in the United States, the Secretary of Agriculture appointed an international panel of BSE experts to review the US BSE response and to make recommendations on the US national program. The panel defined Specified Risk Materials (SRM) as those that are considered to represent the greatest BSE exposure risk to humans and animals because they contain infectivity at some point during the disease incubation period. Blood was not identified as a SRM (Kihm et al., 2004). Numerous international organizations include blood and plasma products in Category IV; tissues with no detected infectivity (DEFRA, 2001; OIE, 1998; SSC, 1997; WHO, 1997).

These data indicate that BSE infectivity is not present in bovine blood of BSE infected cattle.

### **B. The Harvard-Tuskegee Risk Assessment demonstrates that feeding bovine blood will not spread BSE in the cattle population.**

The Harvard Center for Risk Analysis and the Center for Computational Epidemiology at Tuskegee University released the findings of a major 3-year initiative (Harvard-Tuskegee Study) to develop a risk assessment model that allows evaluation of the impact of various risks for exposure of US cattle to BSE (Cohen et al., 2001). The initial report has since been reviewed and updated (Cohen et al., 2002; Cohen and Gray, 2003a; Cohen et al., 2003; Cohen and Gray, 2003b). These reports were extensive and evaluated numerous risk factors associated with the introduction and transmission of BSE.

In the report, the authors recognize that BSE infectivity has never been detected in bovine blood. However, in tissues where BSE infectivity has not been detected, the European Scientific Steering Committee recommends that it should be assumed a minimum BSE infectivity of 10

oral ID<sub>50</sub> / kg (in BSE infected cattle; SSC, 2000). The Harvard-Tuskegee model assumed this level of BSE infectivity was present in the blood of BSE infected cattle. The model also assumed that heifer calves consumed blood from birth while bull calves consumed blood from 7 months to market. Finally, it was assumed that BSE infected cattle existed in the U.S. cattle population. When these assumptions were included in the model, blood contributed on average 0.11 new cases over a 20-year period. The authors summarized:

*“...recycling (feeding) this material (blood) poses little risk of exposing cattle to BSE.”*

The outcome of the Harvard-Tuskegee model shows that when used as a feed ingredient, blood does not contribute to the spread and amplification of BSE in the cattle population.

**C. The detection of TSE infectivity in the blood of other species does not mean BSE infectivity is present in bovine blood.**

Pathology of TSE diseases differs significantly depending on the disease and on the animal model being studied, especially with respect to involvement of the lymphoreticular system (Barclay et al., 2002, Foster et al., 1996, 2001; Wells et al., 1998; Wells, 2003). For this reason, it is not appropriate to speculate that TSE infectivity found in the blood of humans, rodents or sheep proves that BSE infectivity is present in bovine blood. Differences in the distribution of TSE infectivity among tissues of different species of animals make extrapolation among species impossible (Dodd and Busch, 2002; Barclay et al., 2002; Šimák et al., 2002).

The work by UK researchers (Houston et al., 2000; Hunter and Houston, 2002; Hunter et al., 2002) indicated that one sheep of 21 transfused has developed BSE. The EU SSC (SSC, 2002) evaluated the data and concluded (p 6):

*“The TSE ad hoc Group considered that the finding of infectivity in the blood of sheep could not be extrapolated to BSE in cattle. Indeed, the most recent research results do not support the hypothesis that bovine blood or lean meat constitutes a risk for humans.”*

Based on these data it is not appropriate to conclude that detection of TSE infectivity in the blood of other species proves that BSE infectivity must also be present in the blood of BSE infected cattle.

**D. By banning the use of air injection stunning the USDA has eliminated the risk of neural emboli being disseminated in the blood and other tissues.**

Although bovine blood is not inherently infective with BSE, contamination with specific risk material (primarily neural tissue) is possible within the abattoir. Use of various stunning methods and the risk associated with neural contamination of blood and other tissues have been evaluated by several organizations, including the SSC (SSC, 2000, 2002). The SSC (2002) concluded *“Penetrative stunning without pithing appears to be the safest of the three methods of stunning [captive bolt without pithing, pithing, air injection stunning] in regard to the production of CNS emboli.”* USDA FSIS has since banned the use of air-injection pneumatic stunners in the

U.S. (<http://www.fsis.usda.gov/OPPDE/rdad/FRPubs/01-033IF.htm>). The USDA concluded (page 1887):

*“In general, studies have not demonstrated that penetrative captive bolt stunning without air injection results in CNS tissue macro-emboli in the blood or other tissues of stunned cattle.”*

By banning the use of air injection stunning the USDA has eliminated the risk of neural emboli being disseminated in the blood and other tissues.

#### **E. Oral consumption is the least efficient method of transmission of BSE.**

The route of exposure is a major factor determining the efficiency of transmission of BSE. The least efficient method of transmission that has been studied is oral exposure (Kimberlin et al, 1991). Intracerebral injection has been found the most efficient method of transmission. It has been estimated that oral exposure is up to 100,000 times less effective than intracerebral injection. It is important to point out that numerous attempts to detect BSE infectivity in bovine blood involved intracerebral injection. All these attempts have failed to detect BSE infectivity in blood of BSE infected cattle (European Commission Scientific Steering Committee (SSC), April 2000; SSC, October 2000; Bradley, 1993, 1999, 2000; Fraser et al., 1992; Kimberlin and Wilesmith, 1994; Middleton and Barlow, 1993; Moon, 1996).

Injected intracerebrally, BSE infectivity has never been detected in bovine blood. Oral exposure is a method 100,000 times less effective in transmitting BSE. Blood and blood products used in the feed industry are consumed orally.

#### **F. Manufacturing Standards**

As an Industry Group, the NASDBPP are committed to producing a safe, wholesome and effective product. Based on the published scientific data, we conclude that bovine blood does not contain infective levels of the BSE agent. In April 2001, the companies in the United States and Canada involved in the collection and processing of spray dried blood and plasma established a series of Manufacturing Standards. These Standards were established to insure that the blood based products we manufacture do not become contaminated with High Risk Tissues such as brain, spinal cord or distal ileum. These guidelines have been developed and reviewed by internationally recognized BSE experts. Finally, the NASDBPP have contracted with the Facilities Certification Institute (FCI), an independent auditing firm, to annually inspect company facilities to insure compliance with the Industry Guidelines.

These Guidelines have been published for public review (Russell, 2001). In addition they have been presented (formally and informally) to numerous government agencies in the United States and around the world. See **Appendix B** for a more complete description of the NASDBPP Manufacturing Standards.

## G. Summary

BSE infectivity has never been detected in bovine blood. The International Review Team appointed by the Secretary of Agriculture did not include blood in the list of SRM. The Harvard-Tuskegee Risk Assessment demonstrates that feeding bovine blood will not spread BSE. The presence of TSE infectivity in the blood of other species does not prove that BSE infectivity is present in bovine blood. By banning the use of air injection stunning the USDA has eliminated the risk of neural emboli being disseminated in the blood and other tissues. Bovine blood products are fed orally and oral consumption is the least effective method of transmission of BSE. Manufacturing Standards have been developed to insure that spray dried blood and plasma products do not become contaminated with high risk tissues.

In summary, there is no scientific evidence to show that the use of bovine blood or blood products in feed pose a risk of BSE transmission in cattle and other ruminants.

*The economic consequences of banning the use of bovine blood fractions as a feed ingredient are far higher than the ERG estimates of \$60 - \$75 million per year. A ban could cost the beef and dairy industry in excess of \$460,000,000 when considering the reduction in mortality and morbidity that would be realized if these products were widely used.*

### A. Failure of Passive Transfer is a major health problem facing the dairy and beef industry.

Failure of passive transfer (FPT) is a common condition of neonatal dairy and beef calves. Over 41% of the heifer calves raised in the U.S. suffer from FPT due to inadequate colostrum Ig intake (NAHMS, 1992). Others estimate that the prevalence of FPT in young bull calves exceeds 60% (Quigley, unpublished data). The reasons for inadequate colostrum intake are many; however, FPT appears to be an increasing problem in the U.S. In addition, increasing numbers of calves are transported within a few hours of birth, making colostrum availability more problematic for calf growers. Approximately 11% of heifer calves die before weaning and half of this mortality can be attributed to inadequate supply of quality colostrum (NAHMS, 1992, 1996).

Published studies indicate that bovine plasma protein fractions are the only effective alternatives for colostrum (Arthington, et al., 2000a,b; Quigley et al., 1998, 2000, 2001; McCoy et al, 1997; Holloway et al, 2002; Poulsen et al, 2003; Jones et al., 2004; Santoro et al., 2004). For a more complete review of the use of bovine plasma fractions, please refer to **Appendix C**.

### B. Johne's disease is a growing problem in the Dairy Industry that can cost \$245 / cow, translating to \$200-250 million annually.

Johne's disease is a chronic, persistent enteric disease caused by infection with *Mycobacterium paratuberculosis*. Johne's is increasingly recognized as a serious production disease. In the U.S. prevalence of Johne's is increasing and has been estimated to range from about 20% (USDA, 1999) to more than 80% of all dairy herds (Dr. Mike Collins, personal communication; **Appendix D**). Economic losses associated with Johne's disease are estimated at approximately

\$245 per cow inventoried in an infected herd (Ott et al., 1999). Nationally, NAHMS (USDA, 1997) estimated the economic loss to the dairy industry from Johne's disease to be \$200 million to \$250 million annually.

Important vectors for transmission of Johne's include contaminated colostrum and the calving environment. Meylan et al. (1995) reported that a primary route of transmission of Johne's is by consumption of colostrum from infected cows.

Johne's disease control programs on dairy farms require testing of cows. Calves born to cows with positive or presumptive positive tests must be removed from the dam to avoid fecal contamination and must be fed colostrum from test negative cows (Cast, 2001; Kirk, 2000; Sockett, 1996). Unfortunately, many herds are unable to collect sufficient test negative colostrum (McGuirk et al., 2002). Because test sensitivity is less than 50%, there is a significant risk that test negative cattle will also shed the Johne's organism in colostrum and/or feces.

Colostrum replacers containing bovine plasma protein fractions are important tools in Johne's control programs. These products allow producers to immediately separate the calf from the dam and feed a pure, potent, efficacious source of IgG. Since the introduction of colostrum replacers to the industry, producers throughout the Midwest U.S. (primarily Wisconsin, Iowa and Minnesota) have fed these products as the source of IgG. These products have dramatically improved Johne's control programs in the U.S. and are recommended by veterinarians. Recent studies have documented the safety and efficacy of these products (Jones et al., 2004; Santoro et al., 2004).

The only effective replacement for colostrum is bovine plasma protein fractions. If access to these proteins is restricted, there will be no effective alternative to control this disease.

### **C. Alternatives to bovine plasma protein fractions**

There are currently no alternatives for bovine plasma, serum and fractions in colostrum replacers in the U.S. Published literature using colostrum replacers derived from bovine milk or colostrum fail to provide adequate passive immunity in nearly all published studies (see **Appendix C**). The use of alternative sources of colostrum (from test-negative cows) is widely recommended, but many producers have too high prevalence of Johne's in their cows to have sufficient colostrum available. Therefore, the only safe and effective source of IgG for newborn calves is bovine plasma protein fractions.

### **D. Use of bovine plasma protein fractions in calf rearing programs.**

In addition to providing IgG to neonatal calves, immunoglobulins have been used successfully as prophylaxis and treatment of calves.

Several recent published studies have reported reduced morbidity and mortality in calves administered oral bovine plasma protein fractions and challenged with enteric pathogens including *Escherichia coli*, coronavirus, *Cryptosporidium parvum*, and other pathogens (Quigley

et al., 2002; 2003). The use of bovine plasma in reducing effects of enteric infections is summarized in **Appendix E and Appendix F**.

### **E. Economic Losses Associated with Banning Bovine Blood Fractions**

Calf and heifer mortality and morbidity contribute significantly to costs of the heifer enterprise. We include a number of calculations associated with a ban on the use of products containing bovine plasma protein fractions that are currently used in the industry to improve animal health and reduce neonatal mortality (**Table 1**). In each case, we estimate increases in calf morbidity and mortality would be equal to reductions in mortality that have been documented by the use of these products in research. Industry losses associated with Johne's disease have been estimated by the NAHMS report (USDA, 1997). Bovine plasma protein fractions represent critical technologies to manage these problems of FPT and diseases transmitted through maternal colostrum. There are no alternatives for bovine plasma protein fractions.

**Table 1. Economic loss due to FPT and Johne's disease**

|  |        | <u>Heifers</u> | <u>Bull calves</u> |
|--|--------|----------------|--------------------|
| Number of calves <sup>a</sup>                    |        | 4,400,000      | 4,400,000          |
| Number of calves with FPT                        |        | 41%            | 60%                |
| Value of calf, as of July 2004                   |        | \$500          | \$160              |
| Reduced Death loss, per calf <sup>b</sup>        | 12.1%  | \$60.50        | \$19.36            |
| Reduced gain to 28d, per calf <sup>b</sup>       | \$1.53 | \$1.53         | \$1.53             |
| Reduced feed efficiency, per calf <sup>b</sup>   | \$5.70 | \$5.70         | \$5.70             |
| Additional treatment cost, per calf <sup>b</sup> | \$3.74 | <u>\$3.74</u>  | <u>\$3.74</u>      |
| Total, per calf                                  |        | \$71.47        | \$30.33            |
| Cost to industry                                 |        | \$128,931,880  | \$80,071,200       |
| Combined cost                                    |        |                | \$209,003,080      |
| Cost of Johne's Disease <sup>c</sup>             |        | \$200,000,000  | to \$250,000,000   |

<sup>a</sup>[www.fas.usda.gov/dlp/circular/2003/03-12Dairy/toc.htm](http://www.fas.usda.gov/dlp/circular/2003/03-12Dairy/toc.htm)

<sup>b</sup>Fowler et al. 1997. J. Dairy Sci. 80(suppl 1):214; Fowler. 1998. Feedstuffs, June 8, 1998.

<sup>c</sup>USDA. 1997. NAHMS. N245.1097.

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**Appendix A. North American Spray Dried Blood and Plasma Producers**

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Land O'Lakes  
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MS 7405  
St. Paul, MN 55164

Merrick's  
654 Bridge Street  
P.O. Box 99  
Union City, WI 53962

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Sanimal, Inc.  
9900 6e Rue  
Montreal, Quebec H1C 1G2

## **Appendix B. Manufacturing Standards**

Careful collection and processing methods are important to insure that an inherently safe product like blood does not become contaminated with prohibited tissues during collection and subsequent processing. The NASDBPP has developed Manufacturing Standards to insure a consistent, safe product is produced.

Blood is collected from registered abattoirs in the United States or Canada under Federal Inspection. All source animals have been passed ante-mortem inspection as fit for slaughter for human consumption prior to entry into the slaughter facility. Animals showing symptoms of neurological diseases are not allowed to enter the abattoir.

All source facilities process only single species: bovine, porcine or avian. Blood is not collected from abattoirs processing more than one species. This allows blood to be collected with strict species identification. Most importantly this eliminates the potential for accidental sourcing of blood from sheep, goats, deer or mink, species naturally susceptible to TSE diseases.

Some stunning methods have been shown to result in contamination of blood with central nervous tissue (Anil et al., 1999; Garland et al, 1996; Munro, 1997; Schmidt et al, 1999; Taylor, 1996). Neural contamination has not been shown associated with captive bolt stunning. The GMPs developed by the NASDBPP prohibit sourcing of bovine blood from animals stunned by methods shown to result in contamination with neural emboli.

Blood is collected from animals immediately after stunning while the carcass is whole (i.e. before decapitation) reducing the risk of contamination with tissues such as brain, spinal cord or cerebrospinal fluid. Blood is either collected from individual animals or on a stainless steel pan designed to eliminate contamination with other tissues or extraneous material. Immediately after collection the blood is removed from the collection area in a dedicated closed system to a processing and storage area. This area is dedicated to handling of blood only with no other tissues allowed in the area. At the abattoir, blood is stored in dedicated insulated storage tanks prior to transportation to the processing facility.

Blood or plasma is then shipped to off-site spray drying facilities in either dedicated tankers or in tankers certified not to have contained prohibited tissues. This eliminates the potential for contamination of blood with prohibited tissues.

The spray drying facilities are off-site from the abattoir and are dedicated to processing blood or other non-prohibited tissues. Prohibited tissues are not processed at these plants eliminating the possibility of any contamination.

### **Third Party Verification**

The NASDBPP has contracted with Facility Certification Institute to verify member companies are compliant with Manufacturing Standards. On site audits are performed annually.

## **North American Spray Dried Blood and Plasma Producers**

### Guidelines for Blood Collection and Spray Dried Blood and Plasma Processing

1. Blood is collected only from bovine, porcine and avian species in facilities in the United States and Canada which are registered to ship interstate or inter-province and are continuously inspected by USDA/FSIS or Canadian Food Inspection Agency, or a state or provincial inspection authority that has been determined to be equivalent by USDA/FSIS or Canadian Food inspection Agency and slaughter animals for human consumption.
2. Blood is collected only from animals inspected ante-mortem by USDA/FSIS or Canadian Food Inspection Agency, or a state or provincial inspection authority that has been determined to be equivalent by USDA/FSIS or Canadian Food inspection Agency and passed as fit for slaughter for human consumption.
3. All collection facilities are dedicated to one species: bovine, porcine or avian.
4. Bovine blood is collected from facilities certified to stun animals using captive bolt. Bovine blood will not be collected from abattoirs stunning with captive bolt followed by injection of compressed air or captive bolt followed by pithing (see Definitions for complete description of this term).
5. Blood is collected while the animal is whole prior to decapitation and evisceration and in an area where cross contamination cannot occur from exposed internal organs or tissues including nervous tissue or other prohibited tissues (see Definitions for complete description of this term).
6. Blood is transferred immediately from the collection area to a dedicated area for processing.
7. At the abattoir, blood is stored in insulated dedicated storage tanks.
8. Spray drying facilities are isolated and remote from the slaughter facility or any facility that handles prohibited tissue.
9. All transfer lines, pumps and tankers used to transport liquid blood or plasma are dedicated only to blood products or are thoroughly washed (see Definitions for complete description of this term). All non-dedicated equipment is inspected and documented as being thoroughly cleaned (see Definitions for complete description of this term) prior to use with blood products.
10. Spray drying facilities do not co-process, store or utilize any prohibited tissues.
11. Packaging material will be new. If not new, packaging material will be certified to not have contained prohibited tissues or feed containing prohibited tissues. Bulk shipments will be made in dedicated containers or trailers. If the container or trailer is not dedicated, it will be thoroughly cleaned. If the container or trailer can not be thoroughly cleaned or the previous material can not be confirmed, then the product will be clearly labeled 'Do not feed to cattle or other ruminants'.
12. These guidelines are regularly re-evaluated in light of new scientific evidence with regard to natural or experimental BSE.

## Definitions

**Prohibited tissues.** Prohibited tissues shall mean any protein containing portion of mammalian animals, excluding: Blood and blood products; gelatin; inspected meat products which have been cooked and offered for human food and further heat processed for feed (such as plate waste and used cellulosic food casings); milk products (milk and milk proteins); and any product whose only mammalian protein consists entirely of porcine or equine protein.

**Thoroughly washed or thoroughly cleaned.** To use clean-out procedures or other means adequate to prevent carry-over of products that contain or may contain protein derived from mammalian tissues (prohibited material as defined above) into animal protein or feeds that may be used for ruminants.

Also, to maintain written procedures specifying the clean-out procedures or other means and specifying the procedures for separating products that contain or may contain protein derived from mammalian tissue (prohibited material as defined above) from all other protein products from the time of receipt until the time of shipment.

**Pithing.** Insertion of an elongated rod shaped instrument into the cranium through the stun wound.

## Appendix C.

### Effects of Immunoglobulin G Derived from Bovine Plasma on Acquisition of Passive Immunity in Newborn Calves

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#### Executive Summary

Young dairy and beef calves represent the future genetic potential of the farm and constitute a significant economic investment by the farmer. Therefore, their survival and rapid growth are essential to the economics of the farming operation. A key component of the survival and health of calves is colostrum feeding in the first 24 hours of life. Veterinarians and farmers have known for more than one hundred years the importance of colostrum feeding in maintaining the health of young animals, including calves, foals, kids, lambs and pigs. Research has shown that the absorption of IgG in the first 24 hours of life determines the degree of acquisition of passive immunity and subsequent resistance to disease. The USDA estimated that nearly 11% of dairy calves die prior to weaning; most of the mortality can be attributed to inadequate colostrum IgG intake. The USDA also estimated that 41% of dairy heifer calves have failure of passive transfer at 24 hours of age. Amount of IgG absorbed by the calf is determined by many factors, including the concentration of IgG in colostrum, feeding practices of the farm and metabolic state of the animal. Colostrum is widely variable in IgG concentration, and unfortunately, it is difficult to measure colostrum IgG concentration.

The presence of contaminants in colostrum adds a degree of risk to neonatal feeding. Colostrum is recognized as a vector for transmission of a number of disease causing organisms, including *Mycobacterium paratuberculosis*. Farms with significant Johne's infestation often have inadequate supplies of colostrum to feed to their newborn calves. Consequently, farmers are forced to rely on feeding milk replacers and using large amounts of antibiotics to keep the animal alive until its own active immune system can protect it.

The industry has developed colostrum supplements or replacers to improve neonatal and colostrum management. These products are used by dairy producers to increase the IgG

concentrations of colostrum (supplements) or to replace colostrum when it is unavailable or contaminated (replacers). The two sources of IgG for these products are lacteal secretions (milk, colostrum) and plasma. Studies available in the published literature suggest that most supplements derived from lacteal secretions are ineffective in improving the circulating IgG concentration in calves, although they have utility in reducing effects of specific pathogenic challenge. Conversely, IgG in supplements derived from bovine plasma are well absorbed and can contribute significantly to overall circulating IgG concentrations.

Colostrum replacement products contain a minimum of 100 grams of IgG and are formulated to contain nutrition as well as a source of absorbable IgG. There is currently one product available on the market, derived from fractionated bovine plasma. This product is being used in management programs to reduce the spread of economically important diseases such as Johne's disease on farms in the Midwest. Research with the product has shown that feeding one or two doses provides sufficient IgG to provide adequate passive immunity to calves. Survival, health and growth of calves fed the colostrum replacer are similar to calves fed maternal colostrum.

The continued availability of colostrum supplement and replacement products derived from bovine plasma are essential to the industry. Changes in regulations that would prohibit the feeding of blood or blood products to calves would eliminate this important category of product, putting many thousands of calves at risk.

## **Introduction**

In the United States, the sale of cattle and calves and dairy products generated approximately \$38 and \$21 billion in 2002 (USDA ERS, 2003). The dairy and beef replacement enterprises contribute significantly to the total economic output of the farming operation. Indeed, in both dairy and beef operations, production of calves for sale or for replacement animals is an essential part of the operation. Recently, changes in the dairy sector have resulted in development of a unique industry, wherein farms are operated to specifically raise dairy calves as a stand-alone enterprise. These "calf farms" or "calf ranches" have developed rapidly and now contribute to the continued specialization of the dairy industry.

Calves are born with a predetermined genetic potential, which may be permanently affected by management decisions implemented throughout the rearing period and by environmental factors. A calf's genetic potential may be viewed as an upper limit that is expressed only if proper decisions are implemented at the appropriate time. Studies have shown that the level of management has a profound effect on calf morbidity and mortality (Jenny et al., 1981; James et al., 1984; Curtis et al., 1985; Waltner-Toews et al., 1986a, 1986b). Proper management of young stock, particularly during the neonatal period, can markedly reduce morbidity and mortality, whereas improper management will lead to economic losses from increased cost of veterinary intervention, death losses, reduced growth, and suboptimal reproductive performance. In addition, poor management of young stock can reduce the lifetime productivity of the individual cow and the herd as a whole.

The most critical time in the life of the dairy replacement is during the first few days, when morbidity and mortality are greatest. The USDA-APHIS-VS National Dairy Heifer Evaluation Project (NDHEP; NAHMS, 1992, 1996) indicated clearly the inadequacy of current colostrum feeding and management practices. The NDHEP reported that nearly 41% of dairy calves had inadequate circulating concentrations of IgG at 24 h of age. In addition, mortality of dairy calves born alive from birth to weaning was greater than 8%; a follow up study in 1996 (NAHMS, 1996) indicated 11% mortality in the same class of animals. Mortality after weaning was 2.2%. Costs associated with high mortality and reduced productivity are significant. If we assume that approximately 8.1 million dairy calves are born in the U.S. annually and assuming an 11% preweaning mortality, the cost of mortality (assuming an average cost of the calf at \$200) is \$178 million dollars. Not included are costs associated with use of therapeutic and sub-therapeutic antibiotics, lost feed and labor inputs and overhead. The most important factor associated with preweaning mortality is the consumption of colostrum and acquisition of passive immunity within the first 24 hours of birth. The USDA (NAHMS, 1992) estimated that 50% of mortality that occurred in preweaned calves was directly related to inadequate acquisition of passive immunity.

The objective of this presentation is to review the literature related to the acquisition of passive immunity and recent developments in the industry related to colostrum management and feeding and development of colostrum supplements and replacers.

### **Absorption of Immunoglobulins**

Absorption of intact macromolecules across the intestinal epithelium into the neonatal circulation is possible for approximately 24 hours after the calf is born. The absorption of Ig occurs by an active process of pinocytosis, which moves Ig (and other molecules) across the intestinal epithelium. After leaving the epithelium, Ig molecules move into the lymph and then to the circulation. Maturation of the small intestine begins shortly after birth and the ability of the intestine to absorb macromolecules without digestion is lost by about 24 hours after birth. This loss of absorptive ability appears related to the development of the digestive apparatus in intestinal epithelial cells and turnover of cell populations. After about 24 hours of age, the chance to provide the calf with antibodies is gone.

*Failure of passive transfer.* Traditionally, determination of successful transfer of passive immunity has been by measuring the concentration of IgG in the serum of the calf at 24 to 48 hours after birth. If the serum IgG concentration exceeds some critical level, then the calf is thought to be relatively well protected against pathogens. The critical level for determining failure of passive transfer of immunity (**FPT**) is usually considered at 10 g/L (1,000 mg/dl), although some researchers have defined FPT as 8 to 10 g of IgG (or IgG<sub>1</sub>)/L of serum or plasma, and others indicate that <10 g of IgG is indicative of FPT (Blood and Radostits, 1989; Hancock, 1985; McGuirk, 1989; Odde, 1986; Wittum and Perino, 1995). Calves with less than 10 of IgG/L of serum are at greater risk of disease than calves with greater serum IgG concentrations. Of course, the concentration of serum IgG is a continuum of risk – that is, calves with <10.1 of IgG/L of serum are not at markedly greater risk than calves with 9.9 g of IgG/L. Generally, it is well accepted that the greater the concentration of IgG in the circulation of calves at 24 to 48

hours after birth, the greater the protection against the array of pathogens to which the calf might be exposed.

### **Calculation of IgG needs for newborn calves**

There are many factors that influence the concentration of IgG in the blood of the calf at 24 to 48 hours. These include:

- Mass of IgG consumed
- Apparent efficiency of IgG absorption (**AEA**)
- Plasma or serum volume of the calf

These factors can be summarized as:

$$\text{Serum IgG (g/L)} = \text{IgG consumed (g)} \times \text{AEA (\%)} / \text{serum volume (L)} \quad [1]$$

Equation [1] can be used to calculate the efficiency with which IgG are absorbed:

$$\text{AEA (\%)} = \text{serum IgG (g/L)} \times \text{serum volume (L)} / \text{IgG consumed (g)} \quad [2]$$

Intake of IgG is a function of colostrum quality and amount ingested:

$$\text{IgG consumed (g)} = \text{Volume of colostrum consumed (L)} \times \text{IgG concentration (g/L)} \quad [3]$$

Apparent efficiency of IgG absorption is the proportion of ingested IgG recovered in the circulation shortly after cessation of macromolecular IgG transport (closure), usually at 24 to 48 h after birth. Because absorbed IgG equilibrate with non-vascular liquid pools, AEA cannot equal 100%. Most research suggests approximately a 1:1.2 ratio of vascular to non-vascular liquid pools in the neonate (Kruse, 1970; Payne et al., 1967; Wagstaff et al., 1992); therefore, maximal AEA is approximately 45% in neonates. The concept of AEA is not well understood by many veterinarians or nutritionists, but encompasses many of the concepts universally accepted as important to successful passive transfer. For a complete review of factors that affect AEA, see Quigley and Drewry (1998).

### **Colostrum and Ig intake**

Colostrum, defined as the lacteal secretions from the mammary gland during the first 24 h after birth, has long been identified as the primary source of passive immunity for particular species with epitheliochorial placentation. The importance of acquisition of adequate passive immunity is well established – effects of passive transfer on neonatal morbidity, mortality, and performance (growth, efficiency) have been documented extensively. For various reasons, the acquisition of passive immunity may be inadequate, and the risk of morbidity and mortality are increased.

The concentration of Ig in colostrum varies according to the cow's disease history, volume of colostrum produced, season of the year, breed, and other factors (Foley and Otterby, 1981).

Research from Washington (Pritchett et al., 1991) indicated the average concentration of IgG<sub>1</sub> in colostrum from 919 Holstein cows was 48.2 g/L with a range of 20 to >100 g/L. Others reported colostrum concentrations ranging from 32.1 g/L (n = 25; Andrew (2001) to 76.7 g/L (n = 77; Tyler et al., 1999). Jersey (Quigley et al., 1994b) and Guernsey (Tyler et al., 1999) cows generally produce colostrum with greater concentrations of IgG than Holsteins.

Cows exposed to more pathogens produce colostrum with greater Ig than cows exposed to fewer pathogens. Prepartum milking or leaking of milk from the udder prior to calving can reduce the concentration of Ig in colostrum (Roy, 1991). Colostral quality may be affected by transport of IgG from the blood to the mammary gland as well as dilution. Guy et al. (1994) reported that premature lactogenesis caused cessation of IgG<sub>1</sub> transfer into colostral secretions. Possibly, as dairy cattle are bred to produce greater amounts of milk, this contributes to reduced colostral IgG by premature lactogenesis. The negative relationship between colostral volume and IgG was also reported by Pritchett et al. (1994).

Differences between colostral quality in beef and dairy cattle suggest that a relationship between volume of colostrum produced and colostral quality. Guy et al. (1994) reported that reduced IgG<sub>1</sub> concentration in colostrum was associated with greater lactogenic activity in dairy cows, evidenced by fivefold higher alpha-lactalbumin concentration in sera. Dilution of IgG<sub>1</sub> in colostrum may be responsible for breed differences in colostral IgG<sub>1</sub> concentrations.

Variation in Ig content makes accurate colostrum management and feeding difficult. Colostral IgG can be measured in the laboratory with great accuracy; unfortunately, the assays involved are time-consuming and expensive. A measurement of colostrum specific gravity using a device called a colostrometer is one method to estimate Ig content of colostrum (Fleener and Stott, 1980). This device is based on the relationship between Ig in colostrum and specific gravity. Unfortunately, components of colostrum other than Ig affect specific gravity, so the relationship is variable (Quigley et al., 1994b). Also, the relationship between specific gravity and IgG is dependent on temperature (Pritchett et al., 1994; Mechor et al., 1991, 1992). However, the colostrometer may give a qualitative estimate of colostrum quality - particularly if the colostrum is of poor quality. More recent development of lateral flow immunoassay (McVicker et al., 2002) has improved accuracy of prediction of colostral IgG content, but tests are expensive and not widely used.

The amount of colostrum consumed by the calf is the only factor in the equation of serum IgG (equation [1]) that is easily manipulated on the farm. Therefore, many veterinarians and dairy professionals have increased the recommended amount of colostrum in an attempt to reduce the incidence of FPT (NAHMS, 2002; Pritchett et al., 1991). In some cases, up to 8 L of colostrum may be administered by esophageal feeder within the first 24 hours of birth. While this approach serves a useful purpose, it does not address all factors that need to be considered in attempting to maximize successful passive transfer of immunity.

### **Colostrum in transmission of disease**

Colostrum and transition milk have long been known as vectors for transmission of disease in calves. For example, Meylan et al. (1996) reported that a primary route of transmission of

*Mycobacterium paratuberculosis* is by consumption of colostrum from infected cows, although others indicate that ingestion of feces may be the primary route (Streeter et al., 1995; Sweeney, 1996). Because colostrum is identified as a major vector for transmission of Johne's disease, most experts recommend that cows should be tested prior to calving and colostrum from positive or suspected positive cows should not be used to feed to calves. Indeed, Johne's management programs focus on sanitation and management of calves as a means of reducing spread of Johne's (Wells, 2000; Groenendaal et al., 2003). Instead, calves should be fed frozen colostrum obtained from cows that have previously tested negative for Johne's. In herds with many Johne's positive cows, this can often lead to inadequate supplies of colostrum to feed to calves.

Other infective agents identified in mammalian colostrum include bovine immunodeficiency virus (Moore et al., 1996; Meas et al., 2002), bovine leukemia virus (Hopkins and DiGiacomo, 1997), caprine *Mycoplasma mycoides* (East et al., 1983), bovine leukosis virus (Rusov, 1993), *Neospora caninum* (Uggla et al., 1998) and many others.

Modern management practices can lead to significant bacterial contamination of maternal colostrum. Fecteau et al. (2002) reported that nearly 36% of colostrum samples collected from Canadian dairy herds contained at least 100,000 bacteria/mL. Poulsen et al. (2002) reported that 82% of colostrum from dairies in Wisconsin contained >100,000 bacteria/mL and many contained >1,000,000 cfu/mL. Bacterial contamination of colostrum can negatively affect acquisition of passive immunity (James et al., 1981; Poulsen et al., 2002). In addition, colostrum is often stored at room temperature for extended periods on many dairy farms. According to the USDA (NAHMS, 2002), nearly 11% of dairy operations routinely store first milking colostrum (intended as a source of IgG in calves) at room temperature. Another 19% use refrigeration as a means of storing colostrum, which may be inadequate in many situations. Research conducted at the University of California, Davis (P. Jardon, personal communication) showed that when colostrum was left at room temperature, growth of bacteria increased exponentially; indeed, bacterial counts can double approximately every 20 minutes. Within six hours, the number of bacteria in colostrum exceeded 10<sup>6</sup> cfu/mL. These bacteria can markedly affect the health of the calf.

Cow and maternity area are sources of infection for many dairy calves. Numerous researchers have reported increased risk of infection when calves are left in the calving environment for more than a few hours (Jenny et al., 1981; James et al., 1984; Quigley et al., 1994a; Sweeney, 1996). Ingestion of maternal feces has been cited as source of infection for many different calfhood diseases, including Johne's disease, rotavirus, coronavirus, *Cryptosporidium parvum*, among others. Removing calves immediately from the calving environment has been shown to reduce the risk of transmission of several organisms (Quigley et al., 1994a) and is generally recommended by veterinarians. Unfortunately, nearly 44% of calves were left with the dam up to 24 hour after birth (NAHMS, 2002), thereby increasing exposure to fecal contamination.

Another source of contamination in maternal colostrum can come from dry cow treatments with intra-mammary antibiotics. Because it is impossible to predict accurately when a cow will calve, it is likely that some cows will produce colostrum containing antibiotic residues, which can affect the producer's decisions on when and how to sell the calf. Recently, Andrew (2001) reported that the high concentration of fat, protein, IgG and somatic cells in colostrum makes

determination of antibiotic contamination in milk difficult. There were a high number of false positive tests when colostrum and transition milk from cows was tested using commercially available antibiotic screening tests (Andrew, 2001).

### **Effects of pasteurization on colostrum**

One approach to reducing the infectivity of colostrum is through pasteurization. In theory, pasteurization should reduce the level of infectivity of pathogens below threshold levels, thereby reducing the risk of transmission of disease. Traditionally, pasteurization has been used to reduce bacterial counts in waste milk prior to feeding to calves as a source of nutrition (Jumaluddin et al., 1996a, b). More recently, researchers have attempted to pasteurize colostrum prior to feeding within the first 24 hours of life. The primary consideration regarding pasteurizing colostrum is the destruction of pathogens and concomitant destruction of functional proteins, including IgG (Stabel, 2001). Most of the research that has been done to date has explored the effects of pasteurization on the amount of destruction of IgG.

Godden et al. (2003) reported that batch pasteurization (63 C for 30 min) reduced the IgG content of colostrum by an average of 26.2% when compared to pre-pasteurized colostrum samples. There was an effect of the size of the batch, with larger batches (95 L) producing a greater reduction in colostrum IgG content than smaller batches (57 L).

Meylan et al. (1996) also tested effects of batch pasteurization on survival of colostrum IgG, but in a laboratory setting. Their data indicated that IgG in pasteurized colostrum was reduced by more than 12% compared to unpasteurized samples.

Most of the research evaluating pasteurization has used IgG as the indicator molecule for determining the degree of damage caused by pasteurization. However, there are many other proteins in colostrum that may be damaged upon exposure to heat. A few researchers have looked at the effects of heating on other proteins. For example, German researchers (Steinbach et al., 1981) reported that heating colostrum to 55 C for 30 min had no effect on either IgG or IgM; however, heating to 60 C for 10 min reduced IgM dramatically. Others (Liebhaber et al., 1977) reported that pasteurization reduced IgA in human colostrum by 33% and viable immune cells were reduced by over 50%. On the other hand, Jansson et al. (1985) reported that activity of epidermal growth factor was not affected by pasteurization. In light of the uncertainties related to success of pasteurization and concomitant effects on efficacy of pasteurized colostrum, it is difficult to justify widespread recommendation to pasteurize all colostrum.

## **Colostrum Supplements and Replacers**

### **Introduction**

Recognition of high rates of FPT in calves and difficulties in increasing colostrum IgG concentration in cows has led the industry to find ways to provide additional IgG to improve the quality of maternal colostrum. Products used as colostrum supplements were introduced into the market in the mid to late 1980's and have become an important class of product to dairy and beef producers. Colostrum supplement products that contain IgG are regulated in the U.S. by the

USDA Center for Veterinary Biologics. Regulatory approval of products for prevention or treatment of failure of passive transfer requires that products produce an increase in circulating IgG concentration in at least 20 neonatal animals fed a dose of the product above a minimum standard for the specific species (9 CFR 113.499) or to protect the same number of animals against a specific pathogenic challenge (e.g., *E. coli*). Most colostrum supplements approved by USDA have been approved as a means of preventing specific diseases (usually obtained from cows vaccinated with specific vaccines), which requires far less total IgG in the product.

The terms “colostrum supplements” and “colostrum replacers” are poorly defined in the literature and in the industry. Many products are currently marketed as colostrum replacers, but have neither a sufficient mass of IgG nor the nutritional supplementation required by the calf. However, due to the costs associated with collection and processing of raw materials, colostrum supplements have been widely used to completely replace colostrum in the industry. Recent introduction of highly concentrated IgG preparations has allowed discrimination of two classes of products. Quigley et al. (2002a) attempted to define terms to provide more consistent framework within which to regulate and utilize these products.

The term “colostrum supplement” should refer to those preparations intended to provide < 100 g of IgG/dose and are not formulated to completely replace colostrum. Supplements should be formulated to be fed in conjunction with colostrum and to increase IgG concentration and provide nutrients that are inherently variable in MC (e.g., vitamin E).

In addition to an adequate mass of IgG (>100 g of IgG/dose), colostrum replacers must provide nutrients required by the calf. Energy as carbohydrate and lipid is needed to allow the calf to thermoregulate and to establish homeostasis. Digestible protein sources are required as a source of amino acids for gluconeogenesis and protein synthesis, and vitamins and minerals are essential to successful colostrum replacer formulation. Colostrum is a highly concentrated source of fat soluble vitamins, as placental transfer of these vitamins is limited.

There are three sources of IgG for use in colostrum supplements and replacers - lacteal secretions (colostrum and milk), blood and eggs. Each IgG source has different characteristics, advantages and limitations. All are widely available, although the infrastructure for large-scale collection and processing of bovine colostrum is currently limited. The concentration of IgG in bovine milk is quite low and costs of processing to concentrate these IgG are high. Collection of colostrum or milk from other species of animals (sows, mares) is not currently possible in large quantities. Collection and processing of egg IgY is directed primarily to production of antibodies against specific pathogens. Colostrum and blood derived IgG have broad specificity and are more appropriate to production of colostrum supplements. Blood IgG are readily available, inexpensive and well conserved. It should be noted that most IgG in colostrum and milk originate from the blood of cows.

### **Colostrum Supplements**

*Colostrum supplements derived from lacteal secretions.* Colostrum supplements derived from whey and cow colostrum are generally produced by collection of fresh or frozen colostrum from dairy farms for processing. Colostrum may be directly dried (lyophilization or spray-drying) or

processed to remove components (e.g., fat) prior to drying. Other products are produced by concentration of IgG in whey. Supplements are available as powders, pastes and boluses. Haines et al. (1990) reported that the IgG concentration of commercially available colostrum supplements provided between 0.1 to 13.5 g of IgG per dose. Most modern supplement products contain from 25 to 45 g of IgG/dose (a dose is usually 200 to 500 g of powder).

Although colostrum used in manufacturing supplements is obtained from cows on Grade A dairies, these secretions are often collected outside the normal milking parlor; thus there is a risk of contamination from feces, mud and other contaminants from unwashed udders when cows are milked in the maternity area. Colostrum may be stored in different vessels at temperatures that may be undefined and unregulated. It may be transported to the processing facility by means other than those regulated by normal milk handling and processing regulations. It is neither evaluated for numbers of somatic cells nor for the presence of specific pathogens. Further, the risk of infection with mastitis pathogens such as *Staphylococcus aureus* is significant, particularly in colostrum from heifers (Roberson et al., 1998). The presence of antibiotic residues is also significant (Andrew, 2001).

Efficacy of colostrum supplements have been evaluated at several locations. Absorption of IgG from supplements derived from lacteal secretions have generally been reported to be poor (Abel and Quigley, 1993; Zaremba et al., 1993; Garry et al., 1996; Mee et al., 1996; Hopkins and Quigley, 1997; Ikemori et al., 1997; Morin et al., 1997) although the reasons for poor IgG absorption are not defined clearly. Colostrum supplements are designed to be fed in conjunction with maternal colostrum; however, in some experiments (and in application in the industry) colostrum supplements have been fed as a substitute for maternal colostrum.

Abel and Quigley (1993) added a colostrum supplement to maternal colostrum from 32 cows. No effect of colostrum supplement was observed in serum IgG concentrations of calves at 24 or 48 hours after birth. When only the poor quality colostrum samples (<20 g of IgG/L) were evaluated, results were similar. Mee et al. (1996) fed Colostrx® (Schering-Plough, Union, NJ) to four groups of 29 calves. Calves were fed 2 L of bovine colostrum or 500 g of Colostrx mixed in 1.2 L of warm water. In experiment 2, calves were fed either 2 L of colostrum or 500 g of Colostrx in 1 L of water mixed with 1 L of colostrum. In experiment 1, mortality of calves fed Colostrx was 27.6% compared to 3.5% for calves fed colostrum ( $P < 0.05$ ). In experiment 2, there was no difference between treatments, and mean mortality was 13.8 and 3.5% for calves fed colostrum and colostrum + Colostrx, respectively. Serum IgG concentrations at 24 to 36 h after birth were 17.8, 3.0, 18.4 and 9.5 g/L for calves fed colostrum, Colostrx, colostrum (experiment 2), and colostrum + Colostrx, respectively.

Garry et al. (1996) fed normal bovine colostrum or three colostrum supplements (First Milk Formula, Procor Technologies; Colostrx, Immu-Start®, Imu-Tek Animal Health, Inc.) at the rate of 4 L of colostrum or 2 doses (packages) of product. The meals were fed within 2 and 12 h of birth. Serum IgG concentrations at 24 h were approximately 21, 6, 5, and 4 g/L for calves fed colostrum, First Milk, Colostrx, and Immu-Start, respectively. At no point did serum IgG in calves fed any colostrum supplement reach levels indicative of successful passive transfer. Further, AEA was < 10% for all supplements versus >20% for maternal colostrum. These data clearly indicate that none of these products are effective in alleviating the condition of FPT.

Harman et al. (1991) fed newborn calves no colostrum (n = 10), bovine colostrum by suckling the dam (n = 10) or Colostrx (n = 20). Mean serum IgG at 24 h of age were 1.4, 21.0 and 3.7 g/L, respectively.

Hopkins and Quigley (1997) added a colostrum derived supplement (First Milk™ Formula) to maternal colostrum and fed 15 calves. Plasma IgG of these calves at 24 h of age was lower ( $P < 0.01$ ) when compared to calves fed only maternal colostrum and averaged 21.0 and 16.0 g/L for calves fed colostrum or colostrum plus supplement, respectively. The AEA of IgG was reduced from 40 to 30% when the supplement was added.

Morin et al. (1997) also reported no increase in serum IgG<sub>1</sub> concentrations at 24 h when calves were fed 136 or 272 g of a colostrum supplement product derived from dried colostrum in addition to 2 L of poor quality colostrum. These authors also reported marked depression in AEA of IgG<sub>1</sub> when calves were fed 272 g of supplement (18%) vs. maternal colostrum alone (33%).

Hunt et al. (1988), in a review of colostrum supplement products at that time, stated that *“Colostrx should not be combined with colostrum since the resulting mixture is too thick and may be excessively hyperosmotic. Each Colostrx® bag contains a minimum of 24 grams (g) of bovine IgG. This product does not claim to be a total immunoglobulin substitute, and 24 g of bovine IgG represents only one-sixth to one-tenth of the oral immunoglobulin mass necessary to protect calves against septicemic colibacillosis. Electrophoretogram analysis of the mixed solution showed 87% of the total protein present was neither globulin nor albumin, and could not be identified with available laboratory standards... Therefore, much of the product may offer little systemic benefit to the calf, or may represent an immunoglobulin aggregate which we cannot presently identify.*

*Colostrum deprived calves fed Colostrx® absorb such low levels of measurable bovine immunoglobulin that they must still be considered to have FPT[A]”.*

Chelack et al. (1993) fed 9 calves spray-dried colostrum or frozen-thawed pooled colostrum. The spray-dried product provided 126 g of Ig and was reconstituted in 3 L of water. Serum IgG concentration achieved at 48 h of age were 11.6 and 10.6 g/L for calves fed colostrum and spraydried colostrum, respectively. The calculated AEA at 10% serum volume was 45 and 47%, respectively. These data suggest that products for treatment of FPT derived from whey and/or processed colostrum (i.e., lacteal secretions) can, indeed, provide sufficient IgG if they are formulated, manufactured, fed and managed properly.

These data indicate that most current products derived from whey or processed colostrum do not provide significant IgG when fed according to normal recommendations. Data of Chelack et al. (1993), however, indicate that it is possible to achieve normal serum IgG concentrations with sufficient mass of properly processed IgG derived from colostrum sources.

*Supplements derived from chicken eggs.* Preparations derived from chicken eggs have been evaluated in some studies (Erhard et al., 1995, 1997). Typically, these preparations contain IgY obtained from hyperimmunization of chickens. However, absorption of the IgY into the

circulation appear to be relatively low and, therefore, these preparations may be most useful in post-closure applications (Erhard et al., 1997).

*Supplements derived from bovine serum.* A colostrum supplement based on serum proteins (Lifeline, APC, Inc., Ames, IA) is significantly more effective in providing circulating IgG and improved survival of neonatal calves when fed alone or added to maternal colostrum (Arthington et al., 2000a,b; Quigley et al., 1998, 2000, 2001). Immunoglobulin preparations derived from bovine plasma have the advantage of ease of collection, high degree of governmental oversight (all blood is collected at USDA FSIS inspected abattoirs), and available methods to fractionate the IgG. A summary of research conducted with Lifeline as a colostrum substitute is in Table 1.

Other studies have evaluated the use of Lifeline in conjunction with maternal colostrum. McCoy et al. (1997) fed calves within 3 h of birth colostrum of various quality with different amounts of Lifeline to provide equal IgG intake. Mean serum IgG concentrations 12 h after feeding were 6.72 and 10.5 g/L for calves fed colostrum, colostrum + Lifeline, respectively.

**TABLE 1. Plasma IgG and apparent efficiency of absorption (AEA) in calves fed colostrum supplement containing bovine serum.**

| <b>n</b>   | <b>Plasma IgG (g/L @ 24 h)</b> | <b>AEA</b> | <b>Author</b>           |
|------------|--------------------------------|------------|-------------------------|
| 10         | 6.5                            | 15         | Quigley et al., 1998    |
| 12         | 8.3                            | ...        | Arthington et al., 2000 |
| 10         | 6.8                            | 28         | Arthington et al., 2000 |
| 8          | 5.7                            | 30         | Davenport et al., 2000  |
| 48         | 6.5                            | 20         | Quigley et al., 2000    |
| 14         | 8.4                            | 25         | Quigley et al., 2001    |
| 20         | 7.4                            | 33         | Quigley et al., 2001    |
| 16         | 7.4                            | 33         | Quigley et al., 2002a   |
| 11         | 10.6*                          | ...        | Quigley et al., 2002b   |
| 12         | 6.4                            | ...        | Holloway et al., 2002   |
| <b>161</b> | <b>7.3</b>                     | <b>24</b>  |                         |

\*Included Jersey calves.

Holloway et al. (2002) reported that calves fed Lifeline had lower serum IgG concentrations at 2 days of age (6.4 g/L) compared to calves fed maternal colostrum (33.5 g/L). However, the authors noted that the supplement product had similar efficacy to routine colostrum administration practices.

### **Colostrum replacers**

Concentration of IgG from bovine plasma is widely reported in the literature and

many different techniques exist for fractionation of IgG. Large scale fractionation of plasma by APC to produce bovine serum albumin for pharmaceutical production has led to the availability of highly purified IgG for use in animal applications. Using this raw material, APC has developed a highly concentrated IgG product and has made it available in the marketplace in the U.S. The product (Acquire, APC, Inc., Ankeny, IA) contains a sufficient dose of IgG (125 g of IgG per dose) to provide adequate passive immunity. The product is also formulated to contain highly digestible protein, carbohydrates and lipids needed for neonatal thermoregulation and optimal IgG absorption. Numerous trials have been conducted to measure the absorption of IgG from calves fed only this colostrum replacer product (Table 2). In all cases, mean circulating IgG concentration exceeded average minimal IgG concentration for successful passive transfer. In addition, several trials have evaluated calf survival and health of calves. Poulsen et al. (2003) fed colostrum or the replacer product to calves on eight dairy farms in Wisconsin and reported that acquisition of passive immunity (measured by the proportion of calves with FPT) did not differ between calves fed maternal colostrum (n = 142) or those fed the colostrum replacer (n = 147). In addition, there were no differences in mortality or number of veterinary interventions required between groups to 14 days of age. Jones et al. (2004) fed calves (n = 79) either pooled maternal colostrum or colostrum replacer at equal IgG intakes. Concentration of plasma IgG at 24 hours of age were similar between groups and mortality, morbidity and growth to 29 days of age were unaffected by treatment. Quigley et al. (2001) reported similar morbidity and mortality to 60 d of age in calves (n = 160) fed either maternal colostrum or colostrum replacer. These data suggest that the potential exists to replace colostrum with highly concentrated preparations of bovine plasma.

Colostrum replacers are particularly useful on farms with aggressive Johne's eradication programs. The product provides a safe and effective alternative to potentially infected colostrum.

### Summary

**TABLE 2. Plasma IgG and apparent efficiency of absorption (AEA) in calves fed colostrum supplement containing bovine Ig concentrate\*.**

| <b>n</b>   | <b>Plasma IgG (g/L @ 24 h)</b> | <b>AEA</b> | <b>Author</b>         |
|------------|--------------------------------|------------|-----------------------|
| 40         | 10.7                           | 31         | Quigley et al., 2001  |
| 12         | 13.6                           | 20         | Quigley et al., 2001  |
| 39         | 14.0**                         | 20         | Jones et al., 2004    |
| 16         | 13.3                           | 30         | Quigley et al., 2002a |
| 11         | 13.9                           | ...        | Quigley et al., 2002b |
| 29         | 10.8                           | 30         | Hammer et al., 2004   |
| <b>148</b> | <b>12.2</b>                    | <b>26</b>  |                       |

\*Mean IgG intake = 186 g.

\*\*Included Jersey calves.

Management of colostrum is essential to maintaining health of calves and productivity and profitability of the dairy enterprise. Unfortunately, it is clear that colostrum is often deficient in IgG concentration and/or may be contaminated with economically important disease-causing organisms. Thus, the need exists for supplementing or replacing colostrum to enhance the survival and health of young dairy and beef calves. Colostrum supplement and replacement products have been introduced to provide IgG to these animals. Products available in the market are derived from lacteal secretions or bovine plasma. Published literature suggests that supplements and replacements derived from bovine plasma are highly effective in improving the survival and health of young calves, thereby improving the economics of the dairy and beef operations. These products fill an important niche on most farms and their continued availability are essential to continued profitability of the dairy sector.

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## Appendix D.



January 22, 2004

Dr. Stephen Sundlof Director, Center for Veterinary Medicine Food and Drug Administration  
7519 Standish Place Rockville, MD 20855

Dear Dr. Sundlof,

Thank you for the opportunity to express my support for Secure® and its important role in control of Johne's disease. I realize that the current BSE scare is forcing re-examination of the risks and benefits of using bovine blood derived immunoglobulins to feed calves. I speak with authority on the prevalence, economic impact and potential human health and food safety concerns regarding *M. paratuberculosis*, the cause of Johne's disease. I also have first hand experience with the benefits of Secure® in programs to control Johne's disease on dairy farms. As a veterinary microbiologist, I also understand the perception by some that use of bovine blood derived products to feed calves presents some measurable risk. or perhaps a perception of risk, of BSE transmission. My summary opinion is: 1) that the Johne's disease problem in U.S. cattle is real and serious, 2) the benefits of Secure® in Johne's disease control are clear and important, and 3) the risks of BSE transmission from blood derived products originating from cattle in a country where no native BSE cases have ever been detected in spite of a concerted effort by USDA-APHIS to detect BSE cases in the U.S. by testing of thousands brains from downer cows, is realistically and statistically as close to zero as can be imagined.

*Mycobacterium paratuberculosis* infects an estimated 80% of U.S. dairy cattle herds (USDA-NAHMS Dairy 2002 survey, preliminary data reported to the National Johne's Working Group) and 8% of U.S. beef cow-calf herds. This agent seriously impacts the profitability of dairy herds. USDA economists estimate that for herds with a 10% or higher infection rate owners lose over \$200 per adult cow in the herd annually.

*M. paratuberculosis* is also being regularly detected in humans with Crohn's disease, a disease with almost identical epidemiology, pathology and clinical signs as Johne's disease in cattle. Bull et al. reported in July 2003 that 92% of Crohn's disease patients were IS900 PCR positive and 42% were culture positive for *M. paratuberculosis* (J. Clin. Microbiol.). Milk, meat and surface water contaminated with *M. paratuberculosis* from cattle are all plausible vehicles for transmission of this potentially zoonotic pathogen agent to humans. Pasteurization of milk appears ineffective at killing this very thermal-resistant agent. Cull dairy cows infected with *M. paratuberculosis* have a mycobacterial septicemia but are not detected at slaughter and so

processed and sold to consumers as ground beef. Filtration and chlorination are not able to remove or kill *M. paratuberculosis* in surface waters processed for domestic consumption. Control of human exposure requires control of the agent at its source, infected cattle. Control of paratuberculosis is vital to the animal agriculture as well as public health. Interruption of *M. paratuberculosis* infection transmission cows to their off-spring is critical. Colostrum is an important mode of infection spread. Use of alternative sources of colostrum, free of *M. paratuberculosis*, is an important part of a Johne's disease control program. Field trials at the University of Wisconsin proved that Secure® is effective at providing immunoglobulins essential for growth of healthy calves. This product is now routinely recommended as part of a comprehensive Johne's disease control program. All 10 dairy herds on a field trial I am conducting to evaluate Johne's disease control methods are using this product.

It is my sincere hope that both FDA and USDA will make sound science-based decisions as they respond to the single case of BSE detected in a Canadian cow found in the state of Washington. Over-reaction can have long-term harmful consequences far eclipsing the true impact of this imported BSE case. To illustrate this point the table below contrasts BSE and Johne's disease.

|   | BSE  | Johne's disease   |
|---|--|---|
| Herd prevalence in U.S.   | < 1 in 1,000,000                                 | 80%   |
| Cow prevalence in U.S.  | < 1 in 1,000,000                                 | 5%  |
| Prevalence of human-associated disease in the U.S.                      | <1 in 1,000,000 people (vCJD)                    | 1:800 people (Crohn's disease; Mayo clinic, 1998 survey)  |
| Incidence of human-associated disease in the U.S.                       | stable   | rising  |
| Controls to prevent potential human exposure via foods of animal-origin | High risk tissues not used for human consumption | None: Infected cows continue to be used for meat and milk |

A move to prevent production and use of Secure® would not alter BSE transmission risks in the U.S. in any measurable way. It would, however, eliminate a valuable tool in efforts to control Johne's disease, a disease that is far more common and with much more serious human health risks. If FDA is committed to making science-based decisions, they should continue to allow production and sale of Secure®

Sincerely,



Michael T. Collins, DVM, PhD Professor of Microbiology

## **Appendix E.**

### **Effects of Spray-Dried Plasma in the Diets of Calves, Pigs and Poultry**

**J. D. Quigley<sup>1</sup>, J. M. Campbell, C. J. Hammer, J. D. Crenshaw and L. E. Russell**  
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## Executive Summary

Spray-dried animal plasma (SDAP) is a product produced by careful collection, processing and spray-drying of blood collected from government inspected abattoirs. Methods used to collect and process SDAP result in a product that contains functional proteins, including immunoglobulin G (IgG), which can provide intestinal immunity when consumed orally.

Spray-dried animal plasma contains approximately 15% IgG, which is composed of antibodies with titers against economically important diseases. These antibodies are partially resistant to digestion and a significant proportion reach the intestine. Antibodies (IgA and IgG) are an important component of the intestinal immune system and research has shown that circulating IgG moves from the circulation into the lumen of the intestine to inhibit binding of pathogens. Research in calves, pigs, rodents and humans indicates that intestinal Ig (produced locally or transported into the intestine) are a key part of the overall intestinal immune response. In addition, SDAP contains other functional proteins, including growth factors such as insulin like growth factor 1 and transforming growth factor beta, which have been shown to improve cellular growth, particularly in animals following intestinal damage.

Spray-dried animal plasma is widely used in diets for young animals, particularly young pigs. It has been estimated that over 90% of pigs in the U.S. are fed SDAP in their weaning diets. Many veterinarians and nutritionists consider SDAP an essential ingredient to reduce weaning stress, improve intake, reduce the incidence and severity of diarrhea and replace antibiotics in the diet. The functional proteins in SDAP serve as a “first line of defense” against enteric pathogens and work with the immune system to reduce the detrimental effects of these common challenges.

Recent research with broilers and turkeys demonstrate that poultry also respond to the addition of SDAP to their diets. Significant improvements in both rate and efficiency of growth have been reported. In addition, in the face of a respiratory challenge (*Pasteurella multocida*) mortality was significantly lowered when serum proteins were added to the drinking water.

Reducing the reliance on sub-therapeutic antibiotics is a goal of animal agriculture. Many producers have identified the use of SDAP as a means of reducing the dependence on antibiotics without impairing health or growth of animals.

## Introduction

Blood and plasma proteins have long been recognized as high quality feed ingredients for farm animals, including swine, cattle, and poultry. Blood proteins are readily available and have an excellent amino acid profile and high digestibility. Indeed, plasma has been recommended for use in animal diets for hundreds of years – not only as a source of protein, but also as a source of immunological support. Prior to the development and widespread use of antibiotics in animal agriculture, proteins such as egg yolk, blood and colostrum were used as a source of immunologically active proteins to help animals recover from disease. Further, use of blood proteins in animal diets removes this by-product stream from environmental contamination and can increase the value of the animal to the farmer.

Traditionally, proteins were considered simply sources of amino acids for the animal. However, increasingly, scientists recognize that some proteins retain biological activity in the animal – these are called *functional proteins*. Functional proteins are recognized as having some function in the animal that elicits a physiological response. Spray-dried animal plasma (SDAP) is an ingredient widely used in animal feed applications. Several important functional proteins are retained in SDAP that can improve animal survival, health and performance of animals.

### **Method of collection**

Blood proteins have traditionally been collected and heated to high temperatures in the manufacture of blood meal, which destroys the functional components. Conversely, spray-drying preserves the functional characteristics of the proteins, including biologically active peptides, such as albumin and IgG. In this process, blood is collected into stainless steel tanks, troughs or other devices containing an anticoagulant in abattoirs under government inspection. Blood is only collected from animals determined to be fit for slaughter for human consumption by government veterinary inspection. The blood is then transferred to stainless steel tanks, followed by centrifugation to separate plasma from the cellular fraction and chilled to 4-5°C. Chilled plasma is then transported by dedicated equipment to off-site dedicated facilities where it is spray-dried to produce a light brown, freely flowing powder that may be used in feed applications. Recently, the North American Spray-Dried Blood and Plasma Producers Association was formed to establish policies and Manufacturing Procedures to insure the manufacture of high quality and safe products (Russell, 2001).

### **Characteristics of Plasma**

*Functionality.* The method of processing will influence the degree of biological activity that a protein will retain. Spray-drying plasma maintains the functionality of important proteins in plasma, including protease inhibitors, growth factors and immunoglobulins. Because plasma contains approximately 15% IgG, the functionality of this fraction is biologically meaningful to the animal consuming SDAP. Further fractionation can be used to increase IgG concentration to greater than 90%. Of course, the method of processing and preparation have important effects on the degree of functionality of the proteins.

The IgG in plasma are maintained and are biologically active. The Ig titers reflect the combined immunological history of the animals from which blood was collected and typically reflect both the vaccination and pathogenic exposure history of the animal. Plasma is collected into large lots, therefore, wide swings in Ig titer are avoided. It is of interest that the immunological history of animals (swine and cattle) will change over time; therefore the Ig titers in plasma will change also. (Borg, et al., 2002) Spray-dried animal plasma typically contains a wide array of specific antibodies that can be measured by standard serology tests.

Much research has been done to determine whether Ig from one species of animal may provide immunological support in another species of animal. In the feed industry, bovine, porcine and mixed plasma are available. In several studies, improvements in animal performance have been reported in animals fed either swine or bovine plasma (Campbell et al., 2003; Quigley et al.,

2003). Additionally, a tremendous number of published literature is available that documents the use of IgG (primarily bovine IgG or chicken IgY) as oral therapy in humans.

## I. Use of plasma in animal diets

Spray-dried animal plasma has been included in the diets of commercially reared early-weaned pigs for at about 20 years. Today, the vast majority of all feeds fed to pigs immediately after weaning (pig starters) in the U.S. contain SDAP at the rate of 2 to 10% of the formulation. Most research has reported improved intake, animal growth, feed efficiency and animal health in animals (including pigs and calves) when animals were fed SDAP (Gatnau et al., 2000; Morrill et al., 1995; Kats et al., 1994; Quigley and Bernard, 1996; Quigley et al., 2002, 2003; Van der Peet-Schwering, 1995, 1997). Others have compared SDAP to antimicrobials in diets of pigs (Coffey and Cromwell, 1995; Conde et al., 2000; Torrallardona et al., 2002, 2003) and calves (Quigley and Drew, 2000). We have summarized 47 research trials that used plasma in diets of pigs immediately after weaning – the average improvement in body weight gain, feed intake and feed efficiency were 34, 23 and 9%, respectively. Pigs are very susceptible to anorexia immediately after weaning, therefore, a highly palatable ingredient could make a tremendous difference in animal performance (Ermer et al., 1994). The availability of SDAP in weaning pig diets allowed growers to reduce the age at weaning, and although the overall cost of the weaning ration increased with the inclusion of SDAP, overall return to the producer was improved.

Pigs fed SDAP under low antigenic conditions (excellent hygiene and low exposure to enteric pathogens) showed little improvement in performance when plasma was fed. On the other hand, when pigs were raised in a more “conventional” environment with typical exposure to enteric pathogens (indicated in the study by greater incidence of scours), animals fed plasma grew much faster than those fed the control ration. Coffey and Cromwell (1995) confirmed this finding when they fed pigs diets without or with plasma in “low antigenic” or “high antigenic” conditions. Pigs exposed to greater environmental stressors responded more dramatically to the inclusion of SDAP in the diet. These findings suggest that components in SDAP reduced effects of environmental stress. Likewise, similar observations have been reported in broilers (Campbell et al., 2003) and turkeys (Campbell et al., 2004a).

### **Plasma reduces the effect of enteric challenge**

Numerous studies have been conducted in many classes of animals that indicate that plasma reduces mortality and morbidity associated with enteric challenge.

*Pig challenge studies.* Studies have evaluated the use of SDAP in the diet of pigs challenged with enteric pathogens, particularly *Escherichia coli* and rotavirus, which are economically important pathogens to the swine industry. While a thorough review of all of these studies is outside the scope of this presentation, several trials are particularly instructive. Researchers in the U.S. reported that the administration of water-soluble SDAP reduced the effects of oral

challenge with *E. coli* (Borg et al., 1999). Italian researchers (Bosi et al., 2001) challenged pigs with *E. coli* R88 0.148 at weaning. Pigs were fed for 15 days and intake, gain, feed efficiency and mortality were determined. Feeding SDAP reduced mortality, improved growth and efficiency following oral challenge.

A follow-up study by the same researchers (Bosi, et al., 2004) also reported improved performance in pigs fed 6% SDAP or antibiotic (250 mg/kg colistin + 500 mg/kg amoxycycline) in the diet and challenged with *E. coli* ( $10^{10}$  CFU *E. coli* K88 on d 3 after weaning). These researchers also measured the amount of specific K88 antibody in both the plasma and saliva of the pigs on d 15 after challenge. Interestingly, production of K88 specific *E. coli* antibodies in plasma and saliva were reduced when either the antibiotic or SDAP was included in the diet. These data suggest that animals were not exposed to the challenge organism, and therefore, did not produce antibody.

### **Plasma reduces the effect of respiratory challenge**

Spray-dried plasmas action beyond enteric challenge was recently observed by Campbell et. al, (2004b). In this study, 5-week old turkeys were challenged with  $3.0 \times 10^8$  cfu of *Pasteurella multocida* Type III by swabbing the tonsils. Two weeks (14 d) following the challenge, administering water-soluble serum resulted in reduced mortality associated with the respiratory challenge. Survival of control poult was 65%; however, survival was 95% for poult consuming drinking water containing 1.3% Innavax (water-soluble serum).

### Effects of plasma in lactation feeds

Recently there has been an interest in the addition of SDAP to sow lactation feed. Following parturition feed intake is typically depressed especially when environmental temperature is high (Spencer et al., 2003). In a series of trials by APC, Inc., (reported in Feedstuffs, Volume 73 (40) by staff editor, Tim Lundeen, 2001), dietary SDAP (0.25%) improved feed intake (4.7 kg/d vs 5.0 kg/d), reduced lactating sow weight loss (-23.8 kg vs -21.2 kg), improved number of pigs weaned per litter (9.2 to 9.5) and improved litter weight at weaning (46.6 kg vs 48.3 kg). In addition, reduced days to breeding after weaning was noted (8.7 d to 6.9 d). More recently (2004), in a large trial involving 894 sows, feeding 0.5% SDAP resulted in a significant increase in lactation feed intake (adjusted to 18 d lactation period), especially in PI and PII sows (77.8 kg vs 87.5 kg and 90.6 kg vs 100.0 kg; for PI and PII respectively). Improved litter weaning weight, reduced sow weight loss and reduced days to breeding following weaning are consistent with increased lactation feed intake (Patience et al., 1995).

### Effect of plasma in broiler feeds

Recently a number of researchers have reported that rate and efficiency of growth of broiler chicks are improved when SDAP is included in the feed (Yi et al., 2001; Campbell et al., 2003). In addition, skinless, boneless breast meat yield has been increased when SDAP is fed (Campbell et al., 2003, unpublished data). Currently work is underway to establish minimal dietary inclusion and optimal time periods to feed SDAP in poultry diets.

### Other effects of SDAP

Recent research suggests that the functional proteins in SDAP may play important roles in other biological functions of the animal.

Researchers in Spain fed weanling pigs (21 days age weaning) diets containing 0 or 7% SDAP and measured concentrations of caecal microflora following challenge with *E. coli* (Torraddellona et al., 2002). Counts of *Clostridium* were reduced from 1.56 to 0 log CFU/g of caecal contents when pigs were fed SDAP. Further, concentrations of *Lactobacilli* were increased with SDAP in the diet (8.83 vs. 8.01 log CFU/g).

Modification of bone mass in pigs fed SDAP after weaning has also been reported (Jiang et al., 2000), as well as a significant reduction in intestinal weight in rats (Moreto, 2001, unpublished data) and pigs (Jiang et al., 2000). Jiang et al. (2000) also reported reduced urea N concentrations when pigs were fed SDAP postweaning, and suggested that changes in intestinal mass and cellularity was related to changes in circulating urea N concentrations. Plasma or purified globulin fed to pigs has been shown to reduce the concentration of circulating IgG in pigs (Campbell et al., 2000, unpublished data). Bosi et al., (2004) reported that the inclusion of SDAP protein or antibiotics reduced concentrations of IL-8, TNF- $\alpha$  and IFN- $\gamma$  in the jejunum in pigs challenged with *E. coli*.

When taken collectively, these data suggest that dietary SDAP may serve as a “first line of defense” against enteric pathogens, including viruses and bacteria. This “passive enteric immunity” reduces stimulation of the immune system under modern commercial animal production. The animal’s immune system is not over-stimulated, and as a result, pro-inflammatory cytokines secretion by macrophages is reduced. Cytokines secreted by macrophages affect many tissues and are responsible for liberating nutrients for use in supporting an immune response. Recent reports (Touchette et al., 2002) indicate that feeding SDAP reduced secretion of TNF- $\alpha$ , IL-6, and IL-1- $\beta$ . When the immune system is not overstimulated, more nutrients are available for tissue accretion. According to many researchers, SDAP may serve an antimicrobial role in the intestine (Jiang, et al., 2000), thereby reducing the overall enteric challenge.

Constituents in SDAP have also been reported to improve repair of damaged intestinal epithelial tissue in vitro (Rhoads et al., 2000) and in humans (Lembcke et al., 1997). Reports of improved intestinal integrity in pigs challenged with enteric pathogens (Torrallardona et al., 2002; van Dijk, 2001a,b) are also consistent with these observations. It is not yet clear which component(s) are responsible for the observed improvements in regrowth of damaged tissue.

Research continues to elucidate an important role for the functional proteins in SDAP in animal agriculture and potentially, in human nutrition and health. The urgent need to reduce the overuse of antibiotics in diets of animals demands that viable alternatives be found. Numerous published research trials have documented the value of SDAP in reducing the effects of experimental and on-farm enteric challenges.

### Summary

Use of SDAP is well-accepted in animal agriculture. The value of functional proteins, including IgG, to support enteric health, reduce the effects of pathogenic challenge and reduce morbidity and mortality are well documented in both scientific and popular literature. Although not reviewed in this paper, the use of functional proteins (especially IgG) to improve human health is also well documented.

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## “SETTING TOMORROW’S STANDARD”

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Steven F. Sundlof, DVM, Ph.D.  
Center of Veterinary Medicine  
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7500 Standish Place  
Rockville, MD 20855

Dear Dr. Sundlof:

Recent BSE issues have called into question the present FDA regulation permitting the use of milk protein, blood proteins, gelatin, and plate wastes in animal feeds. The economic livelihood of the members of the Professional Dairy Heifer Growers Association (PDHGA) depends upon calf health.

Calf health is dependent upon colostrum supplements, colostrum replacers, and having specialty feeds for use during stress. Our industry depends upon products derived from blood. All these products contain antibodies that help keep calves healthy, particularly early in a calf's life.

Sound science should be the basis of further action, if any, to make changes in the current feed ban. The PDHGA has no political agenda, unlike some that are calling for a ban on the use of blood meal in feed. Our continued use of feed derived from blood promotes good calf health, reduces calf mortality, and improves the economics of heifer production.

Again, we support your use of science as in the past, which has shown no danger of BSE transmission from blood, and for a science-based approach to any changes in the feed ban.

Sincerely,

Larry Jordan  
PDHGA President

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**“HEIFER GROWERS DEDICATED TO GROWING HIGH QUALITY DAIRY REPLACEMENTS”**



02/09/2004 11:50 AM

Dean Cliver <docliver@ucdavis.edu>

To: jim.quigley@amerprotcorp.com,

cc: Mel.Vandenberg@proliantinc.com, jmaas@ucdavis.edu, gbwest@ucdavis.edu

Subject: Re: Value of blood proteins for calves

Dear Dr. Quigley:

I have reviewed the information supplied by you (and also by Mel Vandenberg) and have made some further inquiries of my own. I surmise that the colostrum-and milk-replacer products that your company produces are valuable to the health of calves, particularly at a time when feeding antibiotics is increasing prohibited.

I have determined that bovine blood has never been a Specified Risk Material in the UK, where every possible precaution is being taken to control BSE because the risk is much greater there than anywhere in the world. Despite prolonged and extensive testing, no BSE infectious material has been detected in blood. The FDA took cognizance of this in 1997, when they specifically exempted blood from the feed ban.

A week ago today, a report was published by the “[US] Secretary’s [of Agriculture] Foreign Animal and Poultry Disease Advisory Committee’s Subcommittee on the United States’ Response to the Detection of a Case of Bovine Spongiform Encephalopathy.” The report is very thorough in regard to which parts of cattle should be designated as Specified Risk Materials. The word “blood” does not appear in the report.

I understand that your products are prepared from bovine plasma, and that the absence of blood cells might be perceived as an additional safety factor with respect to transmission of BSE. However, even products made from whole blood should be completely BSE-safe, given the evidence cited above. What is probably most important about your products is that they afford significant protection to calves’ health.

Since I see no scientific basis for the FDA-proposed ban on products such as yours, I believe that such a ban would be a net detriment to animal health and eventually to human health. Evocations of “prudence” and the undefinable “precautionary principle” are usually excuses for ignoring science in favor of cosmetic gestures. Although your company appears to be victimized by the present measures, you are certainly not alone. This is a situation where everyone loses.

Sincerely,

Dean O. Cliver