Report

of the

Irish Medicines Board

to

The Minister for Agriculture & Food

on the availability

of

Intramammary Products

September 22nd, 1999

Contents

1. INTRODUCTION

Concerns regarding the availability and use of antibacterial substances in animal husbandry has led to the incremental introduction of series of controls on the availability and use of such substances in Ireland over the past 20 years. The concerns expressed related to two aspects:

- the risk to the consumer of residues remaining in animal tissue and produce
- the emergence of drug-resistant strains of bacterial pathogens and the consequences of such resistance for animal and human health.

The first significant measure to restrict availability was the Poisons Regulations 1982 (S.I. No. 188 of 1982) introduced by the Minister for Health that effectively restricted the sale or supply of antibacterial substances to pharmacists and veterinary surgeons in respect of animals under their care. A scheme for licensed sellers, operated by the Health Boards, allowed for the sale of intramammary preparations for the treatment and prevention of mastitis. These measures were followed by the Animal Remedies (Control of Sale) Regulations 1985 (S.I. No. 258 of 1985) and the Poisons (Control of Residues in Foods of Animal Origin) Regulations 1985 (S.I. No. 257 of 1985), which were introduced by the Minister for Agriculture and Food. These latter regulations confined the sale and supply of veterinary medicines consisting of, or containing, antibacterial substances to pharmacists in accordance with the terms of a veterinary prescription and to veterinary surgeons in respect of animals under their care. At the time of the introduction of these regulations the principal concern in relation to antibacterials in farm animals related to the risk posed by residues of these substances in the produce of animals intended for human consumption. In recognition of the strict self-regulation imposed by registered co-operative societies in relation to antibiotic residues and their role in promoting mastitis prevention and control programmes amongst their suppliers, intramammary products intended exclusively for the prevention or treatment of bovine mastitis were exempted from the prescription only requirement. These regulations were supplemented by the Poisons (Amendment) Regulations 1986 (S.I. No. 424 of 1986) which restricted eligibility to sell intramammary preparations to registered co-operative societies operating a mastitis control programme. The net effect of these regulations was to restrict the sale and supply of intramammary preparations to veterinary surgeons, pharmacists and specifically licensed registered co-operative societies.

The Minister for Agriculture and Food received various submissions from interested parties on the adequacy or otherwise of current control systems regarding the supply of intramammary products and sought the advice of the Irish Medicines Board (IMB) on the matter in 1997.

The IMB requested its Advisory Committee for Veterinary Medicines (ACVM) to produce a report on the issue. The IMB endorsed a proposal from the ACVM to set up a working group and appointed Ms. M. Waters, Member of the IMB to chair the group. The initial meeting was held on 9th October 1997. The terms of reference of this group are detailed in Appendix 1 and the members of the group are given in Appendix 2. A total of seven meetings of the sub-committee were held and a report was prepared for ACVM for its meeting on 20th September 1999. This report was subsequently adopted by the IMB on 22nd September 1999.

2. MASTITIS

Mastitis is an inflammation of the udder that can occur with or without clinical signs. Infection with bacteria is the major cause of mastitis. Predisposing factors include teat abrasions and sores, poor environmental hygiene and damage from faulty milking machines. Mastitis is the single most important disease of dairy cows and can also affect suckler animals. The disease may be clinical or sub-clinical. Sub-clinical infections occur without any visible signs of infection. There is an increased influx of inflammatory cells (somatic cells) and proteins to the udder resulting in compositional changes in the milk and also reduced yield. If untreated, sub-clinical mastitis may advance to clinical disease. Clinical disease results when there are visible changes in the milk or udder quarter. In addition to inducing an increased cell count, sub-clinical mastitis also reduces the lactation yield and has an adverse effect on milk quality.

Clinical mastitis may be mild (sub-acute), pronounced (either acute, where the affected quarter is hot, sore or swollen) or, chronic (where long-standing infection has resulted in scarring of the udder) or severe (per-acute). Per-acute clinical mastitis is characterised by the presence of clinical signs of illness in the cow caused by bacterial toxins entering the animal's systemic circulation. The causal agent of clinical mastitis can seldom be identified on the basis of clinical signs with the exception of summer mastitis and occasionally coliform mastitis. For other cases, the clinical signs are similar for many different mastitis pathogens.

2.1 Mastitis in Ireland

There are no current authoritative figures on the incidence or prevalence of mastitis in Irish dairy cows. A number of limited studies conducted between 1960 and 1980 indicated that 30% to 40% of cows were affected with mastitis, mainly the subclinical form of the disease (Nyhan, 1963; Egan and Meaney, 1982; Egan and O'Dowd, 1982). Milk somatic cell count data available over this period from dairy co-operatives also indicated a high level of mastitis in dairy herds. These figures were not published or collectively made available by the co-operative movement, but were available from individual registered co-operative societies on a confidential basis.

There is no doubt that sub-clinical mastitis levels in Irish dairy herds has decreased dramatically during the 1990's, largely as a result of culling of cows affected with mastitis. Since the introduction of the milk super levy most dairy farmers have been in a position to cull cows for mastitis. Mastitis continues to be one of the primary reasons for culling cows from dairy farms as indicated in a number of studies. Milk somatic cell count (SCC) data collected by the Department of Agriculture and Food, from their monitoring of dairies supplying liquid milk, show a dramatic decrease in milk somatic cell counts during the period 1989 to 1995. Although these samples relate only to liquid milk, it is likely that this is the trend throughout the entire milk production sector.

Gram-positive bacteria form the majority of isolates present at drying off in dairy cattle. In an infection survey in Irish dairy cows in the period 1984 – 1989, the major bacterial pathogens isolated were *Staphylococcus aureus* (61%), *Streptococcal* species (28%) and non-haemolytic *Staphylococcus* species (6%) (Meaney, 1993).

2.2 Mastitis Treatment

Antibacterial therapy of clinical mastitis is directed to achieving rapid elimination of the infective agent and thereby limiting progress of the disease and suffering of the animal. This also limits the spread of infection to other udder quarters of the same animal or to other animals in the herd.

Intramammary antibacterial medicaments are syringes which are pre-filled with antibacterials. They are designed to administer antibacterials locally into the mammary gland following infusion through the teat duct and *via* the teat canal. There are both preparations for use to treat clinical mastitis in lactating cows and preparations to administer to non-lactating (dry) cows to treat any existing subclinical infection and to prevent the establishment of new infections during the dry period. Intramammary syringes may contain narrow or broad-spectrum antibacterials. Some preparations for use in lactating cows also contain corticosteroids to help reduce inflammation within the udder.

Intramammary antibacterial therapy is a practical means of treating mild clinical cases of mastitis as well as serving as an adjunct to systemic therapy in more severe cases. Per-acute cases require urgent veterinary intervention to save the life of the animal. Therapy of per-acute cases will almost certainly include systemic antibacterials as well as supportive therapy, e.g., rehydrative fluids and anti-inflammatory drugs. Chronic cases of mastitis do not respond readily to therapy and such animals are best culled.

Antibacterial drugs have been used in mastitis treatment since the 1940's. Mastitis appears to be at least as common today as it was before the introduction of antibacterials. However, the types of bacteria causing these infections have changed. The mastitis pathogens highly susceptible to penicillin G (e.g., *Streptococcus agalactiae*) were practically eliminated in many countries, whereas the incidence of mastitis caused by *Staphylococcus aureus* and "environmental" pathogens (e.g., *Streptococcus uberis* and *Escherichia coli*) has increased. The increase in the incidence of *S. aureus* was associated with the increased use of milking machines and the increased incidence of "environmental" pathogens associated with intensification.

The infected mammary gland is the primary source of contagious mastitis pathogens including *Staphylococcus aureus, Streptococcus agalactiae, Corynebacterium bovis* and *Mycoplasma* species. Exposure of teats to these pathogens occurs mainly during the milking process and in the absence of appropriate control measures, these pathogens may infect 50% of all quarters in a herd (Smith, 1999). Environmental mastitis arises primarily from the constant exposure of teat ends to *Streptococcus uberis, Escherichia coli* and *Klebsiella* species from the environment in which cows live (Smith, 1999).

Most mastitis cases are treated by the intramammary route. Antibacterials may also be given by injection and in some cases this may lead to higher cure rates as it allows greater penetration and distribution of the antibacterial within the udder. Clinical cures are readily apparent but without the complete elimination of the pathogen the animal is a potential source of infection for other animals in the herd.

It is difficult to obtain a bacteriological cure in chronic staphylococcal infection; the net bacterial cure rates following treatment are probably less than 20% during lactation. In a limited study of five intramammary preparations commercially available in Ireland, Meaney (1981) found bacteriological cure rates for staphylococcal mastitis ranging from 18% to 53%. Higher cure rates (42% to 93%) were obtained for streptococci. The two preparations tested against coliform bacteria gave cure rates of 73% and 83%.

Despite therapy, most infected and inflamed udder quarters remain latent carriers of staphylococci and relapses of infection are common. Treatment of these infections with long-acting antibacterial preparations at drying off gives a significantly higher cure rate than treatment during lactation. The success of treatment can also be related to the age of the animal, with younger animals showing the highest response to treatment. Complete elimination of mastitis from a dairy herd is almost impossible to achieve, but the mastitis incidence can be kept at an acceptably low level.

Sandholm (1990) stated that antibacterial mastitis therapy is unrewarding. The most that can be achieved from their usage is the temporary reduction or suppression of the bacterial population to give the host a chance to cleanse itself of the infection. The cleansing mechanisms are poorly developed in the udder, as re-lapses and re-infections commonly follow antibacterial therapy. Many acute attacks of mastitis are flare-ups of chronic infections. Stress may be the cause of these infections becoming clinical. The acute inflammation becomes suppressed after a while even if the bacteria are not eliminated. It is therefore difficult to judge whether an antibacterial is effective in these situations (Sandholm, 1990).

As a model of mastitis control it is useful to look at the situation pertaining in Scandinavia.

In Denmark, Norway, Finland and Sweden the principles for the use of antibacterial drugs in the treatment of mastitis are similar. In all four countries a veterinarian always initiates the treatment. As a general principle, treatment is initiated with an intramuscular injection of the appropriate drug. In Sweden the farmer is then allowed to complete the therapy with intramuscular injections during the following 3 - 4 days. In 70 -75% of cases the veterinarian also takes a milk sample for bacteriological examination. The therapy is generally started with penicillin. The choice of drug can then be changed on

the second day if Gram-negative bacteria are isolated. In the other three countries the initial intramuscular treatment is usually followed by intramammary treatment for another 1 - 4 days. However, in Denmark the farmer is not allowed to do this on his own unless he has joined a cattle health service programme with monthly veterinary visits to his farm. The farmer can only get access to drugs from his veterinarian. The veterinary surgeon, therefore, has full responsibility for drug use in the dairy cattle population. Every treated case has to be recorded by the veterinarian. In Denmark dry-cow therapy is allowed only after milk sampling has confirmed bacteriological infection or if the veterinarian has observed signs of clinical mastitis in a quarter. In Norway only short-acting products are allowed for dry cow treatment.

In these four countries a low prevalence of resistance in bacterial pathogens, including those isolated from mastitis cases, is reported, a factor largely attributed to the prudent use of antibacterials (Forshell *et al*, 1996).

2.3 Mastitis Control

Mastitis control has been achieved on many farms by the use of the following procedures:-

- Efficient milking equipment
- Post-milking teat disinfection
- Prompt treatment of clinical mastitis
- Dry-period antibacterial therapy
- Maintenance of a good environment (particularly clean, dry bedding) and good milking hygiene
- Culling chronically infected cows (Meaney, 1986).

Nationally, the testing system for somatic cell counts on milk sold from farms indicate a dramatic reduction in somatic cell counts during the 1990's because of the penalty systems operated by major dairies (ICOS, 1999). It was reported that in the period 1993 - 1998 the use of lactating cow intramammaries decreased by 18% in volume terms in Ireland, while the sales of dry-cow intramammaries increased by 10%. It is estimated that around 75% of cows are now receiving dry-cow therapy in Ireland.

There are no recent figures on the uptake of mastitis control measures in Irish dairy herds. While surveys conducted in 1984 (Kinsella, Egan and Austin, 1986) showed a low uptake of some control measures in herds, it is likely that the situation has improved significantly in recent years. However, there are still indications that some critical components of mastitis control are not being applied in herds. For instance, a recent survey conducted by Egan and others (unpublished) has shown that records of antibacterial treatments and disease prevalence were not maintained in 69% of dairy farms. The absence of adequate disease and treatment records, which should be listed in the Animal Remedies Record of each farm, is a major limitation towards implementing any mastitis control programme. The control measures of post-milking teat dipping and total dry-cow therapy are ineffective against environmental infections (Smith, 1999).

3. HAZARDS OF INTRAMAMMARY THERAPY AND CONSUMER RISK

While the development of resistance to veterinary antibacterials in cows is a matter of concern, the primary risk to public health from the use of antibacterials in animals is presumed to be the possible risk of transferring resistant bacteria to humans. Another potential public health concerns include the introduction of antibacterials directly into the human food chain through contamination of milk supplies with residues above the maximum residue limits (MRLs) established under Council Regulation (EEC) 2377/90. Antibacterials and their residues present in milk may interfere with manufacturing processes and lead to hypersensitivity problems in humans. However, it is generally recognised that the combined mechanisms for authorisation of veterinary medicinal products on the basis of criteria of quality, safety and efficacy, including the establishment of a withdrawal period for the product, together with the extensive surveillance for the presence of residues in animal produce and food of animal origin, minimises this risk.

3.1 Antibacterial resistance

Antibacterial resistance occurs where a micro-organism of a certain species survives in the presence of a concentration of an antibacterial substance that is usually sufficient to inhibit the growth of or kill the bacteria of the same species. Resistance may be inherent or acquired. Most drug-resistant organisms have emerged as a result of genetic mutations and their subsequent selection under antibacterial usage pressure. The development of bacterial resistance has been an expected but an unpredictable phenomenon. Acquired resistance can originate from chromosomal mutation or from the acquisition of transferable genetic elements. The presence of the antibacterial substance serves as a selective mechanism favouring the proliferation of the resistant variant. Plasmids, which are small extra chromosomal DNA elements, and transposons and integrons, which are short DNA sequences, can be transmitted and can code for multi-resistance. Several mechanisms have been identified for the transfer of resistance genes between bacteria including conjugation, transduction and transformation. More than one mechanism may operate for the same antibacterial. Micro-organisms resistant to one antibacterial may also be resistant to other similar antibacterials or to unrelated antibacterials.

Factors that influence the antibacterial resistance of bacteria include the use of sub-therapeutic doses, the class of antibacterial used and the duration of treatment. *Using antibacterials for treatment, therapy, metaphylaxis or prophylaxis in human and veterinary medicine and agriculture has exerted an enormous global selective pressure* (Report on qualitative risk assessment by the Committee for Veterinary Medicinal Products, July 1999). *Every administration of an antibacterial must be considered as an opportunity for the further development of resistance and this attitude needs to be registered by those who use antibacterials if clinical problems are to be satisfactorily contained* (opinion of the Scientific Steering Committee on Antimicrobial Resistance, May 1999). Almost all of the antibacterials used in intramammaries are also used in human medicine. Direct contact with animals and the consumption of contaminated

food of animal origin are recognised to be the main routes of transfer of resistant bacteria from animals to humans.

While the use of antibacterials in animal health is an unquantifiable hazard, several professional organisations and scientific bodies have called for more prudent use of antibacterials (Scientific Steering Committee on Antimicrobial Resistance; Committee for Veterinary Medicinal Products; the Microbial Threat Conference, Copenhagen). Moreover, antibacterial resistance in treated cows has obvious animal welfare and economic implications for animal productivity.

3.2 Considerations in use of antibacterial therapy in animals

It has been widely advocated that *all antibacterials administered on farms should be used only as part of a comprehensive veterinary health programme which should be a matter of record and available for inspection. Herd treatment use of antibacterials should only be allowed if no other alternative is available and should be regarded as a failure of preventive measures which requires evaluation and investigation* (Scientific Steering Committee opinion, 1999). It has also been advocated that in food animals, antibacterial use should always be part of, and not a replacement for, integrated disease control programmes, such as Health Herd Surveillance Programmes. Pedersen et al (1999) state that *healthy animals should not be treated with antibacterials. Antibacterials should be regarded as drugs, rather than production remedies. Prophylactic treatment and flock treatment should be reduced as much as possible. It is a goal in itself to use as little antibacterials as possible.*

Nevertheless, the prophylactic use of antibacterial agents plays an important part in the prevention of new mammary infections in the dry period in cows. Jackson (1993) states that *even if bacteriological examination of milk samples could be carried out routinely to select and treat infected quarters, the udder health of herds would deteriorate rapidly unless all infected quarters also received prophylactic antibacterial therapy.* However, inappropriate use of dry-cow treatments may result in adverse effects including an increase in post-calving infection rates.

3.3 The preservation of animal welfare

Mastitis may cause a significant loss of production in animals. Early diagnosis and treatment of clinical mastitis is important in order to increase the rate of recovery and return to normal milk production. Per-acute cases may result in death. Mastitis often leads to early culling of animals which, therefore, fail to reach their full potential.

The antibacterial of choice used for intramammary therapy should be narrow spectrum. Monitoring of treatment should always be carried out. A limited selection of antibacterials, chosen according to the results from bacteriological diagnosis and sensitivity tests, should be used in treatment. It should be noted that inadequate so-called *sensitivity testing* may lead to a greater misuse of antibacterials than no sensitivity testing (Meaney, 1999). Misleading results may arise from improper sampling techniques, sample mislabelling, prolonged and inadequate conditions of transfer of sample to the laboratory, contamination of samples, inadequate culturing and use of improper discs.

Inability to cure *Staphylococcus aureus* is not primarily associated with *in-vitro* resistance but with a variety of complex issues including bacterial dormancy, inability to reach infection site, binding of antibacterial to milk and re-infection. Sensitivity testing in conjunction with bacteriological identification is of great importance in situations where animals are developing clinical and acute infections. Indeed, in certain situations, e.g., mycotic infections, antibacterial therapy is not required.

The introduction of new antibacterials into a herd should not be based on advertisements but on a change in the resistance pattern of the herd. It is essential that records be kept of all animals diagnosed with mastitis and their response to treatment.

The treatment of cows at drying-off with an antibacterial helps to cure existing sub-clinical infections and to prevent new infections during the dry period. However, the large-scale use of broad spectrum antibacterials or combinations of antibacterials may promote the selection of resistance. Nevertheless, the recommendation to use appropriate narrow-spectrum dry-cow therapy remains until alternative methods of protecting cows in the dry-period are available and proven to be efficacious. Recently, alternative therapy, including the use of bacteriocins and teat seals, is being developed and may have potential for mastitis prevention in the future (Meaney *et al.*1999).

3.4 The safe use of intramammary antibacterials

In order for a given intramammary formulation to deliver the expected efficacy, several factors must be considered: -

- The type of mastitis present and the sensitivity of the target pathogen(s).
- The need for correct administration, e.g., complete milk out of the infected quarter, correct insertion of the tube nozzle.
- Attention to hygiene, disinfecting the teat-end before infusion, use of a teat-dip post infusion.
- Full compliance with labelling directions including any directions regarding dosage, dosage interval and course duration.
- Proper storage of the product before use and observance of expiry date.

Moreover, other factors to be taken into consideration in the choice of an intramammary antibacterial include the spectrum of activity of the antibacterial present in the product, whether the product comprises a single or a combination of antibacterials and the diffusion and persistence of antibacterial in the udder. The persistence of an antibacterial may be influenced not only by the quantity administered, but also by the vehicle used in the product. Antibacterials currently authorised include substances from various chemical classes that differ widely in terms of their bacterial spectrum of activity, the mode and site of action and distribution in the udder. The efficacy of therapy is also linked to compliance with recommendations for repeat or associated treatment and management of the animal.

In considering the safe use of an antibacterial, possible risks to the user of the product, e.g., individual hypersensitivity, and, most importantly, risks to the consumer of milk and dairy products by accidental exposure must be evaluated.

Animals that receive antibacterial therapy should be clearly marked to prevent accidental contamination of the milk output of the herd. Misuse of antibacterials in the absence of professional advice and microbiological support may risk both contamination of milk with residues of the drug and compromise animal welfare. In any event, care should be taken to milk treated animals last and to flush the milking equipment with clean water after use.

While it is acknowledged that the dairy industry operates a comprehensive programme of testing for antibacterial residues in milk collected off all dairy farms, the tests carried out are qualitative screening tests. While the sensitivity of these tests is excellent in respect of certain antibacterial classes, e.g., penicillins, it is not equally sensitive to all antibacterial classes. The tests have been developed as screening tests for inhibitory substances and not as quantitative or confirmatory tests for individual antibacterial substances. The tests, by their nature, cannot meet the demanding performance characteristics for method validation to quantify residues at the maximum residue limit (MRL) established by European Union Council Regulation 2377/90, which may be outside the range of sensitivity on the inhibition tests. By contrast, the screening test used may be more sensitive that the MRL for some antibacterial substances.

It follows, therefore, that compliance with the milk withdrawal period of an intramammary antibacterial is paramount and should be capable of verification through adequate record keeping of the drug administered. Reliance on the screening tests alone does not guarantee consumer safety because of the problems of detection and assay sensitivity. Nevertheless, the existence of such tests serves as a useful aid to protect the food chain from violative residues.

In relation to meat residues, the use of intramammary antibacterials is not expected to contribute significantly to residues in edible tissues provided that the withdrawal period for animal slaughter is observed.

4. PROCEDURES FOR THE AUTHORISATION OF INTRAMAMMARY ANTIBACTERIALS

Veterinary medicinal products are subject to European Union (EU) or national product marketing authorisation procedures. These procedures include the evaluation of residue data that may lead to the establishment of maximum residue limits (MRLs) in accordance with Regulation (EEC) 2377/90. Veterinary products authorised nationally by the Irish Medicines Board in accordance with Council Directive 81/851/EEC must meet the quality, safety and efficacy criteria established by Directive 81/852/EEC. Each authorisation specifies the therapeutic indications, the dosage, the withdrawal period and the method of sale and supply of the product. Authorisations are valid for five years and are renewed upon request and submission of necessary information.

4.1 National legislation controlling the supply of intramammary antibacterials

The legislation relating to the manufacture, importation, distribution, sale, supply, possession and use of veterinary medicines applies to antibacterial intramammary preparations. However, special provision is made by means of specific regulatory provisions relating to the sale or supply of intramammary antibacterials.

The principal legislation governing the sale and supply of veterinary medicines is the Animal Remedies Regulations 1996 made under the Animal Remedies Act 1993 which replace previous enactments made under the Animal Remedies Act 1956 and regulations made by the Minister for Agriculture under Poisons Act 1961 relating to the administration and use of veterinary medicines.

The Animal Remedies Regulations 1996, which also transpose into Irish law the provisions of the EU directives on veterinary medicinal products, prohibit the sale of any animal remedy except under, and in accordance with, a licence for such purpose granted by the Minister for Agriculture and Food. The regulations prohibit the sale of an animal remedy unless the IMB has granted it a product authorisation and given force of law to conditions attached to such authorisation.

One of the conditions to be attached to an authorisation is the route of sale and supply and the prescription-only route is mandatory for all antibacterial substances with the exception of antibacterials authorised as *prescription only (exempt)* [POM(E)] by the IMB. In the case of antibacterial intramammary preparations for the prevention and treatment of bovine mastitis, provision is made by the above legislation to waive the prescription-only requirement. The Poisons Regulations 1982 to 1986 remain in force in addition to the Animal Remedies Regulations 1996 and therefore a “B” licence is still required by registered co-operative societies to sell antibacterial intramammaries.

Insofar as antibacterial intramammary preparations are concerned the net effect of both sets of regulations means that they may only be sold or supplied by:-

- Registered veterinary surgeons in respect of animals under their care,
- Pharmacists
- Registered co-operative societies licensed by both the Minister for Agriculture & Food and the Health Board in whose area the registered co-operative society is situated; the co-operative society having met the criteria laid down by the relevant Health Board in the operation of a mastitis control programme.

A number of weaknesses or deficiencies have been identified in relation to the system of supply by the registered co-operative societies. While it is undisputed that the registered co-operative societies have a strong fundamental interest in ensuring the safety and quality of the milk that they purchase, monitoring is centred on farmers who are suppliers of liquid milk. The licence issued under the Poisons Regulations 1982 to 1986 does not restrict the individual co-operative society to supplying intramammary antibacterials to only participants in their mastitis control programme. There is no monitoring carried out in relation to suckler cows that may be treated with preparations supplied by registered co-operative societies. Sales to farmers are on a self-selection basis.

The criteria for granting a 'B' licence, given originally by the Department of Health to the Health Boards, is shown in appendix 3. Based on responses received by the Irish Medicines Board from various Health Boards and practical experiences gained by officers of the Minister for Agriculture and Food in the general enforcement of veterinary medicines legislation, there is a lack of uniformity in the interpretation and understanding at Health Board level regarding the requirements which an applicant for a 'B' licence must meet. To some extent this may be attributed to lack of specificity in the regulations regarding the nature of direction and control and the constituents of the mastitis control programme. Lack of appropriate expertise at Health Board level to fully assess all the components of the programme at co-operative society and farm level would possibly also be a contributory factor.

Both sets of regulations permit pharmacists to engage in what is effectively over-the-counter sale of antibacterial intramammary preparations. In the case of veterinary surgeons, supply is restricted to *bona fide* clients who have consulted the veterinary surgeon in a professional capacity.

4.2 European Union legislation controlling the supply of intramammary antibacterials

There is no specific European Union (EU) legislation addressing the sale or supply of antibacterial intramammary preparations. The provisions of EU veterinary medicines law apply to the authorisation of the preparations by the national competent authority and legislation relating to Maximum Residue Levels must be observed in establishing withdrawal periods for proprietary products.

Council Directive 90/676/EEC lays down general criteria to be observed by Member States in deciding if a particular proprietary product or class of products should be classified as *prescription only*. Arising out of different national rules applying to the supply and prescribing of veterinary medicines by veterinarians within the EU, the provisions of the Directive are interpreted by Member States against their national rules. The term *prescription only* includes direct supply by the veterinarian. This has resulted in the same proprietary medicine being categorised under different classes in different Member States. Where a particular product or class of product is regarded as being borderline for inclusion as a *prescription only* medicine, the decision is influenced both by the availability and feasibility of alternative restrictions and by the level of direct veterinary intervention in terms of clinical diagnosis.

4.3 The method of sale and supply of intramammary antibacterials in other European Union Member States

In the absence of common rules on prescribing of veterinary medicines and other nuances in the national distribution systems, it is impossible to make direct comparisons on the situation pertaining between Member States. Enquires have revealed that some Member States, like Ireland, have strict rules regarding the conditions which must be met before a veterinarian may prescribe or supply a controlled medicine. Others have very scant regulatory provision on this aspect, leaving matters largely to the professional discretion of the prescribing veterinarian.

The Irish rules regarding prescription are, along with the Nordic Member States, the strictest in the EU with a emphasis on direct examination of the animal by the veterinarian in order to make a clinical diagnosis before a medicine may be supplied or prescribed. The most common approach is to require the veterinarian to consult with the owner or person in charge of the animals before prescribing. It is intended that such consultation should be based on the veterinarian being well acquainted with the general health of the herd from the experience of previous visits. The frequency of such visits and how recently the veterinarian must have been on the farm or seen the animal are criteria that are impossible to establish with any accuracy as it is usually not specified by law. In some Member States one or two on-farm visits per year are considered adequate. In other Member States veterinarians are free to supply to any farmer and there is no need for the supplying/prescribing veterinarian to have any clinical knowledge of the animals to be treated or any form of permanent advisory/consultative relationship with the farmer.

Under the Irish regulation of sale and supply of intramammary antibacterials, the amount of information available on which advice to the farmer is based probably equates with or exceeds some of the more liberal prescription regimes in some Member States, e.g., in France, special arrangements are in place to allow co-operatives to supply dry-cow intramammaries under veterinary control in an arrangement similar to the Irish mastitis control programme.

5. CONCLUSIONS

Ideally, in order to ensure prudent use of intramammary antibacterials, a mastitis control programme should be in existence at farm level. This programme should contain the following elements:-

- Application of the recognised principles for mastitis control and prevention
- Good record keeping by the farmer
- Regular bacteriological and resistance monitoring of each herd in the programme.
- Regular visits by the attending veterinary surgeon to advise on optimum methods of control and to monitor antibacterial usage
- In the case of dairy cows, the monitoring of milk somatic cell count records and regular maintenance of the milking machine.

The ultimate goal for responsible use of intramammary antibacterials is that:-

- They should only be used when scientifically justified,
- They should be subject to veterinary prescription control,
- Their use should be conditional on the existence and operation of a satisfactory mastitis control programme outlined above.

This goal is not provided for by current legislation under any of the existing categories of supply. The short-term options for supply of intramammary antibacterials are therefore:-

- To continue with the existing controls on supply.
- To ban use of intramammaries in animals.
- To restrict intramammary antibacterial use in animals to prescription control.
- To restrict intramammary antibacterials to control as *Prescription only medicine (exempt)* products.
- To restrict intramammary antibacterials to control as *Pharmacy sale* products.
- To allow another form of control.

These options are considered in detail below:-

To continue with the existing controls on supply

Allowing the existing situation to continue is not satisfactory and does not conform with current international scientific opinion on prudent use of antibiotics. In particular, the licensed sellers category which exempts intramammary antibiotics from prescription control is difficult to justify in the face of mounting scientific opinion for rational use of veterinary antibiotics. Moreover, current control mechanisms do not give sufficient guarantees of human safety and animal welfare. In this context, it is noteworthy that the mastitis control programmes operated by registered co-operative societies and regulated Health Boards have several shortcomings:-

- Sensitivity testing appears to be greatly under utilised. The decision to test is left to individual herd owners. Herd owners do not need to conduct any sensitivity testing whatsoever. The farmer can self-select the intramammary as a commodity item.
- No standardised procedures are operable for the sensitivity tests conducted. In the absence of verifiable procedures, covering all stages from sample collection through testing, the reliability of the results generated both within and between laboratories is open to challenge.
- The sensitivity testing data generated is not currently stored for retrieval of epidemiological information.
- The choice of the optimum therapy can be influenced by commercial considerations including promotion of gift item which are inappropriate.
- The criteria for the competent authority for licensing the mastitis control programmes are not specific and not uniformly understood by Health Board personnel. Furthermore, the restrictions of the licensing of such programmes to registered co-operative societies may be open to legal challenge.

To ban antibacterials from intramammary use in veterinary medicines

This option, in itself, would not necessarily lead to a reduction in the presence of resistant organisms, as the selection pressure for resistance is multifactorial. Moreover, mastitis would have to be treated either with antibacterials given by injection or by alternative therapy, the efficacy of which is not proven currently. Furthermore, as is noted by McKellar 1998 *such a draconian decision to prohibit their* [all antibiotics] *use in animals would devastate the livestock industry, increase bacterial - including zoonotic - disease and have catastrophic effects on animal welfare.* In the context of this report on the availability of intramammary products, this is not viewed as a realistic option.

To restrict all antibacterials to prescription only control

This option, which could be achieved by revoking the current exemption from prescription for intramammary antibacterials, would almost certainly lead to a reduction in the use of antibacterial therapy for the treatment and prevention of mastitis in cows, while improving compliance with the conditions of the product authorisation. Existing prescription requirements which require a veterinary surgeon to clinically examine the animal or animals in question immediately prior to the issue of the prescription or supply of the product would place enormous manpower pressure on the veterinary profession. The number of veterinary surgeons currently available is unlikely to be sufficient, especially during peak periods of activity, to meet this challenge. The absence of any requirement for a mastitis control programme on each farm to link with the prescription control is viewed as a major weakness

for this option. If this option is chosen, it is recommended that veterinary surgeons should apply the principles of prudent use in the choice and supply of antibacterials. Moreover, it may be necessary to provide for long transitional measures to allow for an increase in the manpower needed to allow veterinarians to attend each case of clinical mastitis.

To restrict intramammary antibacterials to control as Prescription only medicine (exempt) products

This form of control would restrict the supply of intramammary antibacterials to veterinarians and pharmacists. Veterinarians could supply the products to *bone fide* clients without having clinically examined each animal immediately prior to the supply of the product whilst a pharmacist would have to personally supervise each sale. However, if not combined with a mastitis control programme on the farm, this measure alone may not achieve any obvious improvement in the health of animals and milk quality. Moreover, the provision of appropriate veterinary advice and therapy for each clinical situation and farmer compliance with the conditions of each product authorisation may be little better than that currently available under a less restrictive regime.

To restrict intramammary antibacterials to control as Pharmacy sale products

This form of control would restrict the supply of intramammary antibacterials by veterinarians to *bone fide* clients and by pharmacists (but not necessarily by him/her personally) to farmers and the general public. In the absence of a clinical examination of the animal or identification of the causal organism involved and knowledge of the farm and husbandry of the animals, there is little scientific basis for the choice of therapy and this option is no better than that which exists currently.

To allow another form of control

It is possible that a new system for control could be established as an interim measure.

Mastitis in lactating cows can be a complex issue where the selection of the most appropriate antibacterial is ideally made following a clinical examination of the animal by a veterinarian and a bacteriological identification of the causal agent. In practice, it is not realistic to expect that a farmer would call a veterinarian to each individual routine case of mastitis. Moreover, therapy must, in most cases, commence immediately without the bacteriological identification of the causative organism. A prescription type control system would allow for an increased level of responsibility but consideration could be given to whether a clinical examination would be necessary immediately before the veterinarian prescribes intramammary antibacterials. Farmer compliance with the directions for repeat or ancillary therapy and with the withdrawal periods or other precautions of the product authorisation is best achieved under a form of prescription control where the risks to human safety and disease treatment can be outlined by the prescribing veterinarian. The control system should, however, be linked to a herd health or mastitis control programme on the farm.

Intramammary products for dry-cows could also be supplied under a less restrictive prescription control system than that currently defined by legislation. There is little, if any, need for a veterinarian to have to perform a clinical examination on each animal immediately

before dry-cow therapy. The administration of intramammary syringes does not require special skill and in dry-cows there is no indication for repeat use of the product and seldom need for ancillary therapy. The product is given a month or more before the expected date of calving so there is minimal risk of residues in the milk of treated animals. However, access to intramammary therapy should be on the basis of informed choice such as that available from a properly established and audited mastitis control programme or herd health programme.

It is accepted that any change to the current legislative controls on the supply of intramammary antibacterials should be adequately flagged in advance to all parties concerned and would become legally operational after a transition period to be determined by the Minister.

6. RECOMMENDATIONS

- The current authorisation procedure for the licensing of dairy co-operatives by Health Board personnel should be revoked.
- Future legal controls for the supply of intramammary antibacterials should be brought under the control of the Department of Agriculture and Food.
- The Minister for Agriculture and Food consider whether, on the basis of this report, an amendment to the Animal Remedies Regulations 1996 or other legislation is necessary.
- All legislative controls on animal remedies should be consolidated under the Animal Remedies Act.
- The monitoring system for antibacterial resistance currently undertaken by the Department of Agriculture and Food should be extended to include the monitoring of resistance in bacterial pathogens isolated from the udder. The monitoring system should be based on standard methodologies and quality audits. The data collected should be accessible from a central database.
- Legislative action should be taken to eliminate inducements, particularly financial inducements that might encourage the inappropriate supply of antibacterials, including intramammary antibacterials.
- Legislation should be introduced to restrict the advertising of antibacterials for veterinary use to the veterinary and pharmacy professions only.

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Appendices

Appendix 1. Terms of Reference of Sub-Committee on Intramammary Products

1. To advise the Advisory Committee for Veterinary Medicines on the sale and supply of intramammary veterinary medicines, specifically on:-

   - the provisions of relevant legislation, both national and EU
   - preservation of animal health and welfare.
   - their safe use
   - the risk to the consumer
   - possible emergence of enhanced resistance to the active ingredients following use and significance of this to public health.
   - the need for restriction on sale and supply of these products

2. The Chairperson shall, if present, be the Chairperson of the meeting. In the absence of the Chairperson the members of the Sub-Committee who are present should choose one of the members to be Chairperson for that meeting.

3. In performing its functions the Sub-Committee will examine documents and other material relevant to its workings as are made available to it and may consult with other interested parties as appropriate.

4. The proceedings and findings of the Sub-Committee are confidential and remain so until the Advisory Committee for Veterinary Medicines of the Irish Medicines Board and other concerned parties are advised of the outcome of its deliberations.

Appendix 2. Members of the Sub-Committee on Intramammary Products

Ms. Maura Waters
(Chairperson)

Mr. Patrick Brangan, MRCVS.
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Dr. John Egan, PhD., MRCVS.

Prof. Cyril J. Smyth, PhD.

Ms. Ann Scanlon, MVM.

Mr. Brendan Hayes, MPSI.

Secretariat

Mr. J. G. Beechinor, MVM, MRCVS

The Irish Medicines Board wishes to acknowledge the consultative role of Mr. Bill Meaney, M.Sc in providing expertise on mastitis control to the Group.

Appendix 3. Criteria for Health Boards for Licensing the Mastitis Control Programmes

The general direction and control concept involved here would not require the professional person to be present to supervise individual sales. However, applicants must satisfy the Health Board that general direction and control is being exercised at the retail outlet to which the licence is to relate. The level of supervision being exercised may be measured by an examination, *inter alia*, of the following:-

- The presence of the professional person's dated signature in the antibiotics register showing his comments on the manner of keeping of the register.
- The availability of any guidelines laid down by the professional person setting out products, and circumstances in which, sales may or may not be made.

Furthermore, if the antibiotics register or storage arrangements are found to be unsatisfactory or out-of-date stock is discovered, or antibiotic or other products which the applicant is not lawfully entitled to sell are found, it can reasonably be assumed that the level of professional supervision is not satisfactory.

The Mastitis Control Programme

A limited description of the requirements for a mastitis control programme is included in the Regulations. It will be noted that only programmes operated by registered co-operative societies engaged in the processing of milk are eligible for consideration under the Regulations. In deciding on the adequacy of any particular mastitis control programme proposed for consideration, the following questions, *inter alia*, will need to be addressed:-

- Is the primary objective of the programme the prevention of bovine mastitis and its essential management by the farmer?
- Is the monitoring system in operation and are the laboratory services available sufficient to disclose
  - the presence of antibiotic residues
  - reliable somatic cell counts
  - the sensitivity patterns of the micro-organisms encountered which may cause bovine mastitis
- Is the information generated by the monitoring and laboratory services available to the professional person for decision in regard to the products selected for sale at the particular outlet to be licensed?
- Is there in operation an advisory service capable of providing comprehensive advice in respect of the prevention of bovine mastitis, with particular emphasis on dairy parlour hygiene?
- Is the registered co-operative society participating fully in the scheme introduced in consultation with the Minister for Agriculture under which monetary penalties are imposed on producers who supply milk contaminated with antibiotics?

Applicants for licences under this scheme should therefore be required to furnish a supporting description of the mastitis control programme to be operated by their co-operative society. The programme should be adequately described and details of the arrangements, facilities and personnel available for its implementation should be given.