

Antibiotic Alternatives for Animals



Pressure to reduce antibiotic use, coupled with the EU ban on antimicrobial growth promoters and current debate in the USA, is driving innovation in alternative products that can help reduce, refine and replace antibiotics in farm and companion animals. Market opportunities and regulatory hurdles are highlighted.

Uses of Antibiotics in Animals

Antibiotics are needed in pets and food animals, just as in humans, but efficacy is compromised through antimicrobial resistance and no new antibiotic molecules. The key drivers to reduce consumption and preserve antibiotic efficacy are similar, although arguably stronger, in veterinary than in human medicine, particularly with respect to regulatory hurdles and restrictions in use (Table 1).

Driver	Comments
Antibiotic resistance	Common problem in humans, pets, & food animals Monitoring data (e.g. Danmap http://www.danmap.org) suggest that less use \Rightarrow less resistance
Regulatory restrictions	EU ban on antimicrobial growth promoters Debate on which antibiotics are permitted for veterinary use Debate on restricting veterinarians' rights to prescribe and sell antibiotics
Regulatory hurdles	Trending higher for new veterinary antibiotics
Patent protection	Long time from discovery to market decreases patent life of new molecules
Generic antibiotics	Fast to market on patent expiry \Rightarrow reduced profits from patented molecules
Reduce ROI	Return on investment less attractive for "big pharma"
Divestments	"Big pharma" divestments of veterinary businesses \Rightarrow fewer new veterinary antibiotics
Press/consumer politics	Bad press on antibiotics in farm animals drives consumer demands for "antibiotic-free" food
Supermarkets/competition	Powerful buyers demand "antibiotic-free" food to strengthen marketing platforms
Veterinarians	Veterinarians, especially in pet practices, seek effective alternatives

The animal health world differs from human health scenarios in the way that antibiotics are used, and typical patient profiles. In food animals, whole herd health approaches are the norm. When infectious disease strikes, it is common to medicate the drinking water of the whole herd, to treat affected animals, and prevent healthy animals from contagion. In modern food production systems, typical patients are relatively young, rarely kept beyond adolescence or early adulthood, whereas human antibiotics are used from paediatrics to geriatrics. The relative youth of livestock kept for food has implications for the most common indications of antibiotics. Gut and respiratory infections are common problems in pigs, poultry and cattle. Joint infections are also frequent in farm animals, and skin infections are not uncommon in both pigs and pets. Infectious mastitis is a major problem in dairy herds.

Food animal production systems, whether intensive, extensive, and/or organic, are subjected to stronger market pressures in comparison with human or companion animal medicines. There is a limit on food production costs, largely imposed by supermarket buyers. The cheapest foods tend to arise from the most intensive production systems, with the most economical inputs (e.g. feed, labour, air space, air and water quality). Feed costs may be up to 70% of total food animal production costs, depending on the species, in contrast to the 7% of income that US citizens spend on food. Low-cost generic antibiotics in feed or drinking water have been used for decades to treat farm animals, and indeed most problems, including sub-optimal hygiene and husbandry, improve after

antibiotics. In many cases, antibiotics have been an easy substitute, used instead of better farm management. But now, antibiotics are not welcome any more, and there are opportunities for alternatives.

Nutritional Alternatives to Antibiotics

Nutritional products such as feed additives, feed materials, and complementary and dietetic feeds can support animal health and welfare, and, directly or indirectly, contribute to reducing or replacing veterinary antibiotics. However, no veterinary claims can be made to "prevent, treat or cure" disease. Product positioning and claims strategies are therefore important considerations to be addressed early in new product development, especially where product registration is required. Protection of intellectual property is another important issue requiring appropriate expert advice.

Market Opportunities

Nutritional approaches can be considered as anything given by mouth. An old adage in the feed additive business is "If you can put it in the feed, put it in the feed. If you can't put it in the feed, put it in the feed". Today, application via drinking water may be preferred as a fast, convenient way to administer essential nutritional support, especially in food animals. Nutritional supplements are increasingly applied by spray to newly-hatched chicks or incorporated into gels or granules in chick boxes. Such enriched products improve chick viability and vigour in the crucial hours from hatching through packing and transport to farms for rearing. Innovative coating systems have been developed to protect delicate probiotics during feed processing, and to deliver functional nutrients at target gut sites, bypassing the fore-stomachs in ruminants or offering slow-release in the lower small intestine and large gut of monogastrics. Example of innovations in animal nutrition that contribute to sparing antibiotic therapy are summarised in Table 2.

Type of product	EU legal status	Main modes of action/comments
Better quality feeds	Legally classed as feed materials No pre-market registration required	Improve nutrient digestibility Reduce undesirable hind-gut fermentation
Probiotics	Feed additive registration required	Reduce digestive problems Improve gut flora equilibrium Suppress enteropathogens Improve faecal quality Other benefits
Prebiotics	Legally classed as feed materials No pre-market registration required	Enhance desirable hind gut fermentation
Enzymes	Feed additive registration required	Provide exogenous enzymes Supplement endogenous enzymes Reduce digestive problems
Organic trace minerals	Feed additive registration required	May target specific enteropathogens More bioavailable than inorganic forms Multiple nutritional actions
Natural immune modulators	Most considered as feed materials	Especially effective in aquaculture Opportunities in pets
Organic acids/salts	Feed additive registration may be required	Effective gut hygiene agents Additional benefits from coating
Bacteriophages	Feed additive registration required	Target specific enteropathogens
Botanicals	Feed additive registration required for botanical "extracts"	Appetent effects Zootechnical efficacy Enteric health & gut maturation Bone strength

Better Quality Feeds

Piglets and calves are weaned much earlier in modern than traditional systems and are susceptible to enteric infections, commonly treated with antibiotics. However, improving

quality and innovation in feed ingredients can reduce antibiotic use significantly, by improving feed digestibility and thus the dynamic morphology and physiology of the gut. Examples are the use of colostrum or egg derivatives, high in natural or vaccinal antibodies that help protect the delicate gut mucosa of young mammals. Enzymatic processing of soybean meal to remove anti-nutritional factors enables feeding to a wide variety of young animals, including farmed fish and pets. The resulting soybean meal also has improved mouth feel and palatability, plus a prebiotic effect, since the anti-nutritional factors are converted to beneficial fibres that help develop the right type of hind gut fermentation

Probiotics

Probiotics offer versatile and varied benefits. Robust, spore-forming probiotics survive tough feed processing, whereas more traditional lactic acid bacteria may be applied in drinking water and milk-replacers, or be bound up in complex matrices that improve stability. Presentations miscible in liquid fats and oils can be sprayed on feeds after extrusion, to preserve probiotic viability. Under farm conditions probiotics give consistent improvements in zootechnical performance (growth, feed efficiency), in the order of 2-3% in chickens, and 5-10% in young monogastrics. Probiotics support animal welfare and health by stabilising the gut microflora, improving the quality of gut microbial fermentation (fewer putrefactive micro-organisms and enteropathogens), enhancing faecal consistency (lower water content), and ameliorating adverse environmental effects (reduced excretion of enteropathogens and less ammonia). Hence probiotics may be used in poultry to improve litter quality, and in intensive production systems the reduction in faecal *E. coli* is translated to reduced respiratory infections. Benefits in companion animals include improved faecal consistency, facilitating collection of faeces in urban areas (much appreciated by owners!), and a reduction in veterinary interventions for gastro-enteritis, especially notable in puppies.

Prebiotics

A variety of prebiotic fibres and oligosaccharides are used in animal nutrition, particularly in extruded pet foods. Prebiotics are valued for their stability to harsh feed processing conditions, and their bulking and laxative actions. There is increased interest in developing “dream team” prebiotic-probiotic combinations, to enhance gut health through synergistic actions on the gut flora and faecal quality.

Enzymes

The first feed enzymes arrived in the 1980s and were mostly targeted at digestion of “difficult” carbohydrates in cereals and oilseeds. These exogenous enzymes allowed incorporation of a larger variety of ingredients (e.g. rape, sunflower, triticale, rye) and/or a higher content of cereals in feeds (e.g. barley, wheat). Subsequent enzymatic waves targeted support of endogenous enzymes, such as proteases and amylases, at critical points in development, for example, piglets at weaning. Enzymes, like probiotics, improve the gut environment, but by different mechanisms. Probiotics suppress enteropathogens, and so enhance positive gut microbial fermentation, whereas enzymes achieve a similar effect by rapid and complete

digestion of fermentable substrates, thus preventing adverse fermentation by putrefactive or pathogenic bacteria. A third enzymatic wave, derived from genetically modified producer strains, includes heat-tolerant carbohydrases and phytases. Heat-tolerant enzymes are more stable during feed processing. Phytases improve phosphorus utilisation, and hence increase skeletal strength, with positive environmental effects derived from reduced phosphorus excretion. Recently developed phytases also offer significant improvements in zootechnical performance. A fourth enzymatic wave is expected to target enteric problems by novel, non-antibiotic mechanisms.

Organic Trace Minerals

Organic trace minerals such as chelated copper, iron, manganese, and zinc, or selenium yeasts, offer essential minerals in highly protected and bioavailable forms. Hence absorption and distribution are enhanced with fewer anti-nutritional cross-reactions in the gut. Trace minerals are important in myriads of biochemical processes, and play key roles in supporting the nutritional needs of today’s fast-growing, fast-metabolising food animals. Put simply, inorganic minerals may not supply the needs of such animals to achieve their genetic potential for growth and feed conversion. Skeletal strength is a key attribute in poultry and pigs. For example, high culling rates in breeding sows and boars are often associated with joint and leg problems. More dramatically in broiler chickens and turkeys, bred for “big breast” meat yields, weak leg bones cause lack of mobility and recumbency, leading to breast and skin burns, and bacterial infections of the skin, feet and joints, complicated by poor litter quality (high moisture and ammonia).

Natural Immune Modulators

A number of immune modulators are used, especially in pets and aquaculture. Beta-glucans and nucleotides are two examples from aquaculture. Young farmed fish are subject to many stresses during handling, vaccination, and transfer from freshwater to seawater cages. Nucleotide immunomodulators exert positive effects on gut morphology and function, resulting in higher viability and improved growth rates. Inactivated microbes such as *Lactobacillus spp.* have shown good effects in skin inflammation, atopic dermatitis and seasonal allergies of people and pets. In a study with an inactivated *Lactobacillus acidophilus* strain, dietary supplementation of 4-8 weeks duration in dogs with atopic dermatitis resulted in reduced area and severity of skin lesions, reductions in T cells with type 4-positive C-C chemokine receptors, and reductions in allergen-specific IgE antibodies (Shinji *et al* 2014).

Organic Acids/Salts

Organic acids and their salts have been successfully used for several decades to improve gut hygiene in food animals. More recent developments include fat-based coating systems that reduce handling hazards in feed mills, reduce corrosion of equipment, and deliver effective dosages to target gut sites. The total dose required is also reduced due to the synergism between the protective coating and slow-release microgranules.

Bacteriophages

Bacteriophages targeting specific enteropathogens have aroused interest over past decades, but successful use in animal feeds or drinking water has been challenging. Improved delivery systems and final product stability will help resolve major obstacles to market.

Botanicals

Development of botanicals as alternatives to antibiotics in animal nutrition began in the EU in the 1980s. Since 2010 a few “flagship” products have achieved, or are undergoing, EU registration as zootechnical feed additives, an attractive legal status for investors, resulting in an authorisation linked to the applicant with resulting protection of intellectual property. A zootechnical approval also serves to differentiate the product, as successful evaluation by EFSA (European Food Safety Authority) is viewed globally as an independent guarantee of quality, safety and efficacy. Natural botanicals are complex (Figures 1 and 2), with large variations in quality

and activity of components due to many factors, for example the part/s of plant/s used, type/s of processes applied, as well as geographical origin, harvesting conditions, etc. In the EU there are also borderline issues on the legal status of botanical extracts (or the related terms absolute, essential oil, tincture), classed as feed additives (flavours, colours or zootechnical), and plant derivatives subject to simple processing (e.g. drying/crushing herbs and spices) considered as feed materials. Additionally EFSA and member states have sometimes divergent views on potential toxicity of certain botanicals. Some botanical preparations are based on nature-identical components, which have the advantage of high purity, but the disadvantage in marketing terms of being less “natural”. As with other products destined for in-feed use, a variety of coatings may be used to improve stability of volatile aromatic substances, and to deliver active components to target gut sites. Good quality botanical preparations deliver expected and surprising benefits. Expected benefits, perhaps related to aromatic and appetent properties, include improved feed intake, feed digestibility and animal growth. More unexpected benefits are related to better gut hygiene, reduced enteric problems, faster gut maturation, and improved skeletal strength. Some botanicals are targeted at diseases such as coccidiosis and necrotic enteritis in poultry.

Registration Costs and Time to Market

Feed additive registration costs for antibiotic alternatives can vary considerably, depending on the safety package required, the target species, and other regulatory challenges. Generally speaking, the safety package is considerably less than that required for a new molecule, since many of the active components have a safe history of use in the food chain. As a rough guide, the minimum EU registration cost for a new feed additive preparation destined for broilers is around €250,000, with increments of approximately €150,000 per additional target animal category. Time to market, assuming zero data at project start is three to five years, for generation of data, preparation and submission of an EFSA-compliant dossier, and guidance through EFSA evaluation and EU approval.

Conclusions

The global feed additive market, including feed antibiotics, is estimated to grow at around 4% per annum, and to be worth in excess of €15 billion by 2018. Experience in Europe suggests that there are opportunities to develop innovative alternatives, and it is likely that “antibiotic-free” demands from consumers and supermarkets will drive product development towards nutritional solutions in preference to traditional antimicrobials.

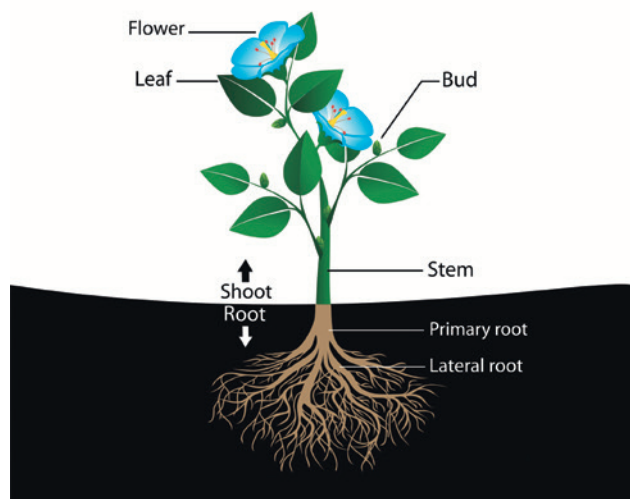


Figure 1

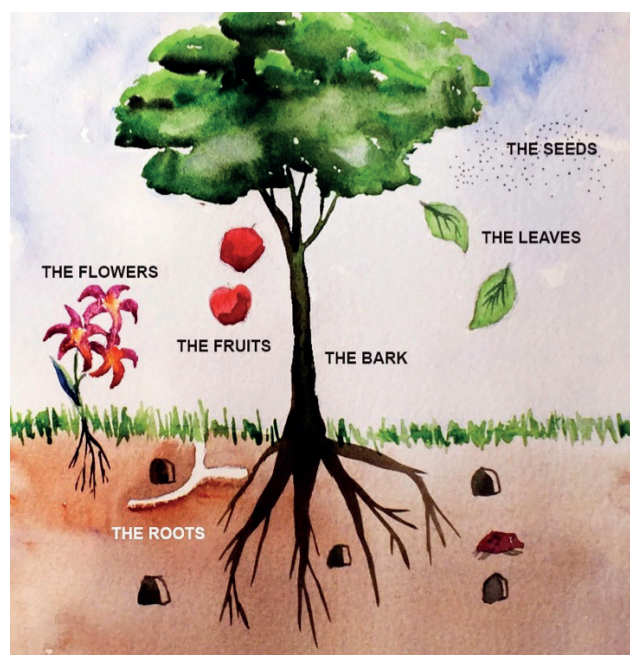


Figure 2



Dr Elinor McCartney, Pen & Tec Consulting Ltd. Elinor McCartney is an expert in EU food chain legislation, with over 30 years experience in development and registration of veterinary, animal health and nutrition products. In 2000 she founded Pen & Tec Consulting, dedicated to strategic and regulatory support of companies wishing fast access the EU market with innovative, non-antibiotic products. Email: elinor@pentec-consulting.eu