

Review

History of the Use of Antibiotic as Growth Promoters in European Poultry Feeds

J. I. R. Castanon¹

Department of Animal Science, University of Las Palmas de Gran Canaria, 35413 Spain

ABSTRACT Use of antibiotics as growth promoters in animal feeds has been permitted in the member states of the European Union during the last 50 yr. However, concerns about development of antimicrobial resistance and about transference of antibiotic resistance genes from animal to human microbiota, led to withdraw approval for antibiotics as growth promoters in the European Union since January 1, 2006. This report analyzes the history of European legislation regarding the use of anti-

biotics in poultry feeds, since the first harmonization by Directive 70/524 until Regulation 1831/2003 deleted these substances from the European Register of additives permitted in feeds. The European support to recommendations of the World Health Organization, the Food and Agriculture Organization, and the World Organization for Animal Health for a ban on antimicrobial use in animal feeds is expected to favor other countries also phase these substances out.

Key words: antibiotic, growth promoter, antimicrobial, history, poultry feed

2007 Poultry Science 86:2466–2471
doi:10.3382/ps.2007-00249

INTRODUCTION

The growth promoter effect of antibiotics was discovered in the 1940s, when it was observed that animals fed dried mycelia of *Streptomyces aureofaciens* containing chlortetracycline residues improved their growth. The mechanism of action of antibiotics as growth promoters is related to interactions with intestinal microbial population (Dibner and Richards, 2005; Niewold, 2007).

The United States Food and Drug Administration approved the use of antibiotics as animal additives without veterinary prescription in 1951 (Jones and Ricke, 2003). Also in the 1950s and 1960s, each European state approved its own national regulations about the use of antibiotics in animal feeds.

European Regulation Concerning Additives in Animal Feeds

European harmonization of regulations concerning additives in feedingstuffs aimed the establishment and functioning of the common market for animal feeds, since national regulations of each member state differed as regards to their basic principles. Council Directive 70/524, published in the Official Journal L 270 of December 14, 1970, underlaid the basis principle of regulation: only

those additives which are named in this Directive may be contained in feedingstuffs and only subject to the requirements set out herein.

The member states, within 2 yr following notification, brought into force the laws, regulations, and administrative provisions necessary to comply with this Directive, and from November 25, 1972, additives, feedingstuffs containing additives and human foods from livestock fed additives were subject only to the marketing restrictions provided for in this Directive. This regulation also applied to other countries of the European Economic Area (Iceland, Norway).

Recently, Directive 70/524 was replaced by Regulation 1831/2003 of the European Parliament and of the Council on additives for use in animal nutrition. Regulation 1831/2003 stated that antibiotics, other than coccidiostats and histomonostats, might be marketed and used as feed additives only until December 31, 2005. Anticoccidial substances, such as antibiotics ionophores, also will be prohibited as feed additives before 2013. After this date, medical substances in animal feeds will be limited to therapeutic use by veterinary prescription. European legislation can be consulted in <http://eur-lex.europa.eu/en/index.htm>

National Authorization Vs. European Authorization

Antibiotics permitted in the European feeds were listed in the annexes to Directive 70/524: annex I listed antibiotics without marketing restrictions in all the European

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Received June 15, 2007.

Accepted July 30, 2007.

¹Corresponding author: jrodriguez@dpat.ulpgc.es

Community, and annex II listed antibiotic that could be allowed by a state within its territory. When the use of certain additives authorized at national level had been widely tested, and the studies carried out and the experience gained indicated that these additives might be authorized throughout the Community for the uses specified, those additives were included in annex I. Annex II constituted therefore an intermediate stage in determining the inclusion of additives in the list of those permitted in the Community listed in the annex I. Annexes to Directive 70/524 were regularly amended in the light of scientific and technical knowledge.

ANTIBIOTIC ADDITIVES THAT WERE PERMITTED IN POULTRY FEEDS

The antibiotics which were authorized to be included in poultry feeds without a veterinary prescription are shown in Tables 1 and 2. Moreover, until December 3, 1986 (Directive 84/587) two authorized antibiotics could be mixed if they did not belong to the same chemical group.

Antibiotics That Were Authorized Only at the National Level

Annex II to Directive 70/524 listed the following antibiotics: bacitracin manganese, neomycin, soframycin (or framcetin), hygromycin-B, tylosin, and erythromycin. These antibiotics could be permitted at national scale with the conditions stated by each state. However, Directive 76/296 withdrew approval for these products after June 30, 1976 (December 31, 1976 for hygromycin-B), except the use of erithromycine in feeds for fattening chicks, which was extended until the end of 1978 by Directive 78/58.

Other antibiotics which were later added to annex II to be used in feeds for poultry (excluding ducks, geese, and laying hens) up to 10 wk old were lincomycin (Directive 74/180, authorized until June 30, 1981) and bacitracin-methylene-disalicylate (Directive 75/267, until December 31, 1977). Also the following antibiotics were included in annex II to be used only in feeds for chickens for fattening: mocimycin (Directive 78/743, until November 30, 1983), nosiheptide (Directive 79/1011, until December 3, 1986) and ardacin (Directive 94/77, until November 30, 1997).

Antibiotics Listed in Annex I to Directive 70/524

Annex I to Directive 70/524 listed the additives permitted in feeds to be marketed in the Community: Member states could not restrict the marketing of the feeds containing these additives. The antibiotics initially listed in annex I to be included in poultry feeds (excluding ducks, geese, and laying hens) were tetracyclines (tetracycline, chlortetracycline, and oxytetracycline) and penicillins (penicillin-G-potassium, penicillin-G-sodium, and peni-

Table 1. Antibiotics which were permitted as feed additives only in national poultry feeds

Antibiotic	Species of animal	Maximum content of additive in complete feeds and period of authorization	Legislative references
Bacitracin manganese, Neomycin, tylosin, soframycin	Only national restrictions	November 25, 1970 to June 30, 1976	Directives 70/524, 75/296
Hygromycin-B	Only national restrictions	November 25, 1970 to December 31, 1976	Directives 70/524, 75/296, 76/603
Erythromycin	Only national restrictions Chickens for fattening	November 25, 1970 to June 23, 1976 20 ppm, June 24, 1976 to December 31, 1978	Directives 70/524, 75/296, 76/603
Bacitracin-methylene-disalicylate	Poultry (excluding ducks, geese, and laying hens) up to 10 wk old	20 ppm, April 29, 1975 to December 31, 1977	Directives 76/603, 78/58
Lincomycine	Poultry (excluding ducks, geese, and laying hens) up to 10 wk old	10 ppm, March 5, 1974 to June 30, 1981	Directives 75/267, 75/296, 76/603
Mocimycin	Chickens for fattening	5 ppm, August 1, 1978 to November 30, 1983	Directives 74/180, 75/296, 76/603, 78/58, 79/139, 79/553, 80/618, 80/1139
Nosiheptide	Chickens for fattening	10 ppm, November 16, 1979 to December 3, 1986	Directives 78/743, 80/1156, 82/91, 82/822
Ardacin	Chickens for fattening	7 ppm, January 20, 1995 to November 30, 1997	Directives 79/1011, 80/1156, 82/91, 82/822, 83/466, 84/349, 85/342, 85/520 Directives 94/77, 95/55, 96/66, 97/72

Table 2. Antibiotics that were permitted as feed additives in poultry feeds for the Community market

Antibiotic	Species of animal	Maximum content of additive in complete feeds and period of national authorization	Maximum content of additive in complete feeds and period of Community authorization	Legislative references
Tetracycline, chlortetracycline, oxytetracycline	Poultry (except ducks, geese, laying hens) up to 10 wk old	20 ppm (50 ppm up to 4 wk) November 25, 1970 to June 30, 1976	20 ppm, November 25, 1972 to August 5, 1973	Directives 70/524, 73/264, 75/296
	Poultry (except ducks, geese, laying hens) up to 10 wk old	20 ppm (50 ppm up to 4 wk) November 25, 1970 to June 30, 1976	20 ppm, November 25, 1972 to August 5, 1973	Directives 70/524, 73/275, 75/296
Penicillin-G-potassium, penicillin-G-sodium, penicillin-G-procain	Poultry (except ducks, geese, laying hens) up to 4 wk old	25 ppm, November 25, 1970 to July 31, 1978 10 ppm, August 1, 1978 to September 30, 1979	10 ppm, November 25, 1972 to March 31, 1976 20 ppm, April 1, 1976 to July 31, 1978	Directives 70/524, 76/13, 76/603, 78/58, 78/743
	Poultry (except ducks, geese, laying hens) between 5 and 10 wk old	10 ppm (25 ppm up to 4 wk) November 25, 1970 to March 31, 1976 to July 31, 1978 10 ppm, August 1, 1978 to September 30, 1979	10 ppm, November 25, 1972 to March 31, 1976 to July 31, 1978 20 ppm, April 1, 1976 to July 31, 1978	
Oleandomycin	Turkeys between 11 and 26 wk old, and other poultry (except ducks, geese, laying hens, pigeons) between 11 and 16 wk old	20 ppm, December 18, 1975 to July 31, 1978 10 ppm, August 1, 1978 to September 30, 1979	20 ppm, December 18, 1975 to July 31, 1978 10 ppm, August 1, 1978 to September 30, 1979	
	Turkeys for fattening up to 16 wk old	20 ppm, February 4, 1982 to April 1, 1997	20 ppm, February 4, 1982 to April 1, 1997	
Spiramycin	Poultry (except ducks, geese, laying hens) up to 4 wk old	50 ppm, November 25, 1970 to December 31, 1978	20 ppm, July 1, 1982 to February 7, 1997	Directives 70/524, 76/13, 76/603, 78/58, 80/678, Regulation 2821/98
	Poultry (except ducks, geese, laying hens) and laying hens) between 5 and 10 wk old	20 ppm, January 1, 1979 to June 30, 1999	20 ppm, November 25, 1972 to December 28, 1998	
Virginiamycin	Turkeys between 11 and 26 wk old, and other poultry (except ducks, geese, laying hens, pigeons) between 11 and 16 wk old	20 ppm, December 18, 1975 to June 30, 1999	20 ppm, April 1, 1976 to December 28, 1998	
	Laying hens	20 ppm, May 17, 1983 to June 30, 1999	20 ppm, June 30, 1989 to December 28, 1998	Directives 70/524, 73/103, 76/13, 76/603, 78/58, 83/266, 85/520, 86/403, 87/552, 88/616, Regulation 2821/98
Bacitracin zinc	Other poultry (except ducks, geese) up to 4 wk old	20 ppm, November 25, 1970 to May 3, 1973	20 ppm, November 25, 1972 to December 28, 1998	
	Other poultry (except ducks, geese) between 5 and 10 wk old	50 ppm, May 4, 1973 to December 31, 1978	20 ppm, November 25, 1972 to December 28, 1998	
	Turkeys between 11 and 26 wk old, and other poultry (except ducks, geese, pigeons) between 11 and 16 wk old	20 ppm, January 1, 1979 to June 30, 1999	20 ppm, November 25, 1972 to December 28, 1998	
	Laying hens	20 ppm, November 25, 1970 to June 30, 1999	20 ppm, November 25, 1972 to December 28, 1998	
	Ducks up to 10 wk old	20 ppm, December 18, 1975 to June 30, 1999	20 ppm, April 1, 1976 to December 28, 1998	
	Other poultry (except ducks, geese, pigeons) up to 4 wk old	20 ppm (100 ppm since December 18, 1975), March 5, 1974 to June 30, 1999	100 ppm, June 30, 1979 to December 28, 1998	Directives 70/524, 74/180, 75/267, 75/296, 76/13, 76/603, 77/471, 78/58, 78/743, 78/974, 94/41, 95/55, 96/66, 97/72, Regulation 2821/98
	Other poultry (except ducks, geese, pigeons) between 5 and 10 wk old	10 ppm, April 29, 1975 to December 31, 1978	Not permitted	
	Turkeys between 11 and 26 wk old, and other poultry (except ducks, geese, pigeons) between 11 and 16 wk old	50 ppm, November 25, 1970 to June 30, 1999	50 ppm, December 31, 1978 to December 28, 1998	
	Other poultry (except ducks, geese, pigeons) between 5 and 10 wk old	20 ppm, November 25, 1970 to June 30, 1999	20 ppm, November 25, 1972 to December 28, 1998	
	Turkeys between 11 and 26 wk old, and other poultry (except ducks, geese, pigeons) between 11 and 16 wk old	Chickens for fattening: 50 ppm, September 1, 1994 to November 30, 1998 20 ppm, December 18, 1975 to June 30, 1999 50 ppm, September 1, 1994 to November 30, 1998	Chickens for fattening: 50 ppm, September 1, 1994 to November 30, 1998 20 ppm, April 1, 1976 to December 28, 1998	

Flavophospholipol	Laying hens	5 ppm, March 5, 1974 to December 31, 2005	5 ppm, June 30, 1979 to December 31, 2005	Directives 70/524, 74/180, 75/296, 76/13, 77/471, 78/58, 78/974, Regulations 2205/01, 1831/03
	Chickens for fattening up to 10 wk old	20 ppm, November 25, 1970 to December 31, 2005	20 ppm, November 25, 1972 to December 31, 2005	
	Chickens for fattening between 11 and 16 wk old	20 ppm, December 18, 1975 to December 31, 2005	20 ppm, April 1, 1976 to December 31, 2005	
	Other poultry (except ducks, geese) up to 10 wk old	20 ppm, November 25, 1970 to May 15, 2002	20 ppm, November 25, 1972 to May 15, 2002	
	Turkeys between 11 and 26 wk old, geese, pigeons) between 11 and 16 wk old Chickens for fattening	20 ppm, December 18, 1975 to May 15, 2002	20 ppm, April 1, 1976 to May 15, 2002	
Avilamycin	Turkeys	10 ppm, July 23, 1990 to December 31, 2005	10 ppm, June 30, 1996 to December 31, 2005	Directives 90/412, 91/620, 92/99, 93/107, 94/50, 95/37, 97/72, Regulation 1831/05
Avoparcin	Chickens for fattening	10 ppm, January 12, 1997 to November 30, 1998 15 ppm, June 24, 1976 to April 1, 1997	Not permitted 15 ppm, January 1, 1980 to February 7, 1997	Directives 76/603, 78/58, 78/974, 79/697, 79/1011, 82/91, 97/6
	Turkeys for fattening up to 16 wk old	20 ppm, February 4, 1982 to April 1, 1997	20 ppm, July 1, 1982 to February 7, 1997	

cillin-G-procaine) in feeds for poultry up to 10 wk old. Also oleandomycin, spiramycin, virginiamycin, bacitracin zinc, and flavophospholipol were permitted in feeds for poultry up to 10 wk old, raised up to 16 wk (26 wk for turkey) by Directive 76/13. Bacitracin zinc was also permitted by Directive 75/267 in feeds for ducks at national level until the end 1978.

Later, virginiamycin, bacitracin zinc, and flavophospholipol were approved for use also in feeds for laying hens, at first at a national scale (Directives 83/266, 74/180, and 78/974, respectively) and finally they were included in annex I by Directive 88/616 (virginiamycin) and Directive 78/974 (bacitracin zinc and flavophospholipol).

Other antibiotics added to annexes to Directive 70/524 to be included in poultry feeds were avoparcin and avilamycin. These products were authorized in feeds for chickens for fattening, at first at the national level (Directives 76/603 and 90/412, respectively) and finally included in annex I by Directives 79/1011 and 95/37, respectively. These products were also permitted in feeds for turkeys for fattening: ardacin was included in annex I by Directive 82/91, and avilamycin was permitted by Directive 97/72 at a national scale until November 30, 1998.

THE EUROPEAN BANS OF ANTIBIOTICS

The risk concerning residues of antibiotics in edible tissues and products that can produce allergic or toxic reactions in consumers is known to be negligible (Donoghue, 2003) because only antibiotics that are not absorbed in the digestive tract are authorized as growth promoters. However, the wider use of antibiotics as feed additives in the long run can contribute to the development of resistant bacteria to drugs used to treat infections. These microbials with resistant genes poses a potential risk for humans if they are transferred to persons. For this reason, the World Health Organization (1997) and the Economic and Social Committee of the European Union (1998) concluded that the use of antimicrobials in food animals is a public health issue.

The Former Bans

As soon as the 1970s, antibiotics from classes which were or might be used in human or veterinary medicine were transferred from annex I to annex II to phase them out after a certain period. It was the case of tetracyclines (Directive 73/264), penicillins (Directive 73/275), and oleandomycin (Directive 78/743), which were placed in annex II to be used only at a national scale in feeds for poultry. This national authorization was limited until June 30, 1976 (tetracyclines and penicillins) or September 30, 1979 (oleandomycin).

The Bans Proposed by Member States and the Sweden Case

A member state which, as a result of new information or of a reassessment of existing information made since

the provisions in question were adopted, had detailed grounds for establishing that the use of one of the additives authorized at the Community scale constituted a danger to animal or human health or the environment could temporarily suspend the authorization to use that additive in its territory, and it should forthwith inform the Commission; member states should not, however, be able to have recourse to that power to hinder the free movement of the products. According to the information provided by the state, a decision on the additive was taken.

Sweden prohibited in 1986 the use in feedingstuffs of additives belonging to the groups of antibiotics. When Sweden accessed in 1995 as a member of the European Union, it was authorized to maintain in force until December 31, 1998, its legislation before accession. Before that date, Sweden submitted applications, accompanied by detailed scientific grounds, for adjustments for the antibiotics authorized in the Community.

Also, other member states prohibited on their territories the use of some antibiotics in animal feedstuffs. Avoparcin was banned in Denmark (May 20, 1995) and Germany (January 19, 1996) arguing that this glycopeptide antibiotic produces resistance to glycopeptides used in human medicine, spiramycin was prohibited in Finland (January 1, 1998) because this product was used in human medicine, and virginiamycin was prohibited in Denmark (January 15, 1998) because 2 streptogramins were clinically important in human medicine.

As results of this national initiatives, Directive 97/6 withdrew approval for Avoparcin from 1 April 1997, and Regulation 2821/1998 banned spiramycin and virginiamycin from June 30, 1999. Regulation 2821/1998 also banned bacitracin zinc because its use in human medicine as treatment of infections of the skin.

The Last Ban

On January 1, 1999, Sweden applied the safeguard clause for the antibiotics still authorized as feed additives, including those still permitted in poultry feeds: flavophospholipol and avilamycin. The scientific ground submitted by Sweden, as well as the conclusions of the World Health Organization (1997) and of the Economic and Social Committee of the European Union (1998), led to no longer to authorize the use of antibiotics as growth promoters: Regulation 1831/2003 stated that antibiotics, other than coccidiostats and histomonostats, might be marketed and used as feed additives only until December 31, 2005; as from January 1, 2006, those substances would be deleted from the Community Register of authorized feed additives.

EXPECTED CONSEQUENCES OF THE BAN

The main expected consequence of the ban is a reduction of the amount of antibiotics used in animal production, and therefore the risk of transferring to persons of microbes with resistant genes to antibiotics. Available

data suggest that the growth-promoter ban has driven an increase in infections and therefore a substantial increase in the use of therapeutic antibiotics for food animals in Europe, but the ban also has reduced overall antibiotic use in animals (Casewell et al., 2003). Wierup (2001) also reported that in Sweden, as a result of the ban and a focus on disease prevention and correct use of antimicrobials, the total use of antibacterial drugs to animals decreased by approximately 55% in the period 1986–1999, and a relatively low prevalence of antimicrobial resistance has been maintained.

In other ways, the ban of growth promoters demands the improvement of the hygiene of farms. It was shown that under good production conditions it is possible to reach good and competitive production results for the rearing of poultry without the continuous use of antibiotics in feeds (Wierup, 2001; Engster et al., 2002; World Health Organization, 2002). Moreover, safer nonantimicrobial substances have been studied as alternatives for replacing antibiotics to interact with the intestinal microflora, including enzymes (Bedford, 2000; Hruby and Cowieson, 2006), prebiotics, and probiotics (Patterson and Burkholder, 2003; Kocher, 2006), or acidification of diets (Ricke, 2003; Diebold and Eidelsburger, 2006).

Finally, the ban of antibiotics in animal feeds will have consequences in the international trade of poultry meat because the European Union only imports foods obtained from animals that were not fed with antibiotics, in application of the precaution principle allowed by the World Trade Organization. However, because concern is rising that drug-resistant pathogens could be transmitted to humans via the food-chain (World Health Organization, 2003, 2004), it is expected that the use of antimicrobials in animal production will decrease in further years, at least in those farms with better hygiene conditions.

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