

## I

*(Acts whose publication is obligatory)*

**COUNCIL REGULATION (EC) No 2821/98**

**of 17 December 1998**

**amending, as regards withdrawal of the authorisation of certain antibiotics,  
Directive 70/524/EEC concerning additives in feedingstuffs**

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community,

Having regard to the 1994 Act of Accession, and in particular Article 151 in conjunction with Annex XV, Title VII(E)(4) thereof,

Having regard to Council Directive 70/524/EEC of 23 November 1970 concerning additives in feedingstuffs<sup>(1)</sup>, and in particular Article 11(3) thereof,

Having regard to the proposal from the Commission,

(1) Whereas the Kingdom of Sweden was authorised under Annex XV to the Act of Accession to maintain its legislation in force before accession until 31 December 1998 with regard to the prohibition of the use in feedingstuffs of additives belonging to the groups of antibiotics; whereas on 2 February 1998 Sweden submitted applications for adjustments accompanied by detailed scientific grounds for the antibiotics avilamycin, bacitracin zinc, flavo-phospholipol, ardacin and avoparcin, spiramycin, tylosin phosphate and virginiamycin; whereas the Commission is required to take a decision on the adjustment applications submitted by Sweden not later than 31 December 1998;

(2) Whereas, under Article 11 of Directive 70/524/EEC, 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, has detailed grounds for establishing that the use of one of the additives listed in the Directive constitutes a danger to animal or human health or the environment may temporarily suspend the authorisation to use that additive;

(3) Whereas the Republic of Finland, after expiry of the derogation granted to it under the Act of Accession, prohibited the use on its territory of tylosin phosphate and spiramycin in feedingstuffs from 1 January 1998 on the basis of the detailed grounds it had submitted on 12 March 1997 under the obligations laid down in the Act of Accession;

(4) Whereas on 15 January 1998 the Kingdom of Denmark prohibited the use on its territory of virginiamycin in feedingstuffs; whereas it communicated the detailed grounds for that decision to the other Member States and the Commission on 13 March 1998 and 1 April 1998;

(5) Whereas, by virtue of Article 3a(e) of Directive 70/524/EEC, authorisation of an additive is not to be given if, for serious reasons concerning human or animal health, its use must be restricted to medical or veterinary purposes;

(6) Whereas the authorisation of the glycopeptide avoparcin was withdrawn on 30 January 1997<sup>(2)</sup> as an interim protective measure taken as a precaution; whereas that prohibition has to be reviewed by the Commission not later than 31 December 1998, on the basis of the results of the various investigations concerning the development of resistance by the use of antibiotics, in particular glycopeptides, and the programme of surveillance of antimicrobial resistance in animals which have received antibiotics, to be carried out in particular by the persons responsible for putting the additives concerned into circulation; whereas, since the Commission has received no new information to date, there is no reason for the prohibition to be reviewed;

<sup>(1)</sup> OJ L 270, 14.12.1970, p. 1. Directive as last amended by Commission Directive 98/19/EC (OJ L 96, 28.3.1998, p. 39).

<sup>(2)</sup> Commission Directive 97/6/EC of 30 January 1997 amending Council Directive 70/524/EEC concerning additives in feedingstuffs (OJ L 35, 5.2.1997, p. 11).

- (7) Whereas it was also decided as a precaution on 12 January 1998<sup>(1)</sup> not to renew the authorisation of another glycopeptide, ardacin, until the results of research still to be carried out on avoparcin were available;
- (8) Whereas the Commission consulted the Scientific Committee on Animal Nutrition (SCAN) on whether the use of tylosin phosphate and spiramycin should for serious reasons concerning animal or human health be restricted to veterinary medicine; whereas after examining the Finnish grounds for prohibiting the said macrolides as feed additives, the Committee stated in its opinion of 5 February 1998 that the data presented did not provide sufficient evidence that the use of macrolides as feed additives presented a significant risk to human or animal health and that, in the absence of sufficient research data on the epidemiology and spread of macrolide resistance, there was no reason for a ban on the use of the substances in question as additives;
- (9) Whereas SCAN acknowledges, however, that the wider use of macrolides as feed additives in the long run will contribute to the overall selective pressure for resistant bacteria to a significantly larger extent than would result from the use of macrolides for veterinary therapy alone; whereas SCAN acknowledges the probability that resistant enterococci or *erm*-resistance genes will be transferred from animals to humans will be higher, the higher the prevalence of resistant enterococci in animals is; whereas SCAN is of the opinion that the possibility that an increase in the resistance pool at animal level might pose risks to humans has been neither proven nor disproved, but that such a risk might be expected to be demonstrated;
- (10) Whereas SCAN also notes that tylosin-resistant enterococci isolated from pigs are almost all simultaneously resistant to erythromycin, an important macrolide antibiotic in human medicine notably in the treatment of respiratory infections; whereas it finds that, even if cross-resistance to lincosamides and streptogramins has not been tested in Finland, macrolide resistance in enterococci is, according to the literature, often or mostly encoded for by different *erm*-genes also conferring resistance to lincosamides and streptogramin B; whereas there is a clinical problem in human medicine if the enterococci resistant to macrolides include also a major resistance to streptogramin B; whereas two lincosamides are in clinical use in human medicine, namely lincomycin and clindamycin; whereas two streptogramins are clinically important in human medicine in the treatment of last resort of vancomycin resistant enterococci, namely pristinamycin and the combination dalfopristin/quinupristin;
- (11) Whereas SCAN also notes that some experiments on mice have shown that *in vivo* transfer of erythromycin resistance from enterococci to other bacteria is possible; whereas it also specifies that erythromycin-resistant animal enterococci may colonise humans for a longer or shorter time period or may transfer their macrolide-resistance genes to the resident bacterial flora of humans, notably to human bacteria such as staphylococci or group A streptococci, which would constitute a clinical problem in human medicine, either directly after ingestion or via gene exchange in the environment, but that the frequencies of such transfers cannot be estimated;
- (12) Whereas, in the light of the various abovementioned factors, the Commission, for its part, takes the view that there are sufficient grounds for a ban; whereas the risk of reducing the effectiveness of human medicinal products such as erythromycin in particular and possibly lincomycin, clindamycin, pristinamycin and the new combination dalfopristin/quinupristin, which is due to be authorised as a human medicinal product shortly, as a result of selection of cross-resistance caused by tylosin phosphate and spiramycin, should be avoided;
- (13) Whereas, moreover, spiramycin is used in human medicine and whereas therefore the resistances selected by the use of spiramycin as an additive increase the pool of spiramycin-resistance which could be transferred from animals to humans and thus make spiramycin less effective in human medicine;
- (14) Whereas the Commission consulted SCAN on whether or not streptogramin-resistant *E. faecium* and staphylococci selected by the use of virginiamycin as a growth promoter constituted a public health risk at present or could constitute such a risk if streptogramins took a pivotal role for treatment of serious human infections in the future;
- (15) Whereas after examining the grounds put forward, the Committee concluded in its opinion of 10 July 1998 that the use of virginiamycin as a growth promoter did not constitute a real immediate risk

<sup>(1)</sup> Commission Directive 97/72/EC of 15 December 1997 amending Council Directive 70/524/EEC concerning additives in feedingstuffs (OJ L 351, 23.12.1997, p. 55).

- to public health in Denmark since Denmark had provided no new evidence to substantiate the transfer of streptogramin resistance from organisms of animal origin to those resident in the human digestive tract, which would compromise the future use of human medicinal products; whereas it stresses that there is currently no need for streptogramins in Denmark as the existing therapeutic treatments for treating enterococci and staphylococci infections are still effective there;
- (16) Whereas, none the less, SCAN acknowledges that a reservoir of resistant genes within the animal population poses a potential risk for humans; whereas, contrary to the Commission, it is of the opinion that a full risk assessment cannot be made until, in particular, quantitative evidence of the extent of transfer of antimicrobial resistance from livestock sources is obtained;
- (17) Whereas SCAN is also concerned about the development of vancomycin resistance amongst enterococci and methicillin-resistant strains of *Staphylococcus aureus*, which are increasingly responsible for nosocomial infections, particularly in the United States and southern Europe; whereas that could make it necessary to use streptogramins as therapeutic agents of last resort to treat germs which have developed resistance to other antibiotics;
- (18) Whereas, furthermore, SCAN notes in its opinion that the virginiamycin-resistant enterococci and staphylococci isolated from poultry and pigs all had cross-resistance to pristinamycin used in human medicine or the combination dalfopristin/quinupristin, which is due to be authorised as a human medicinal product shortly;
- (19) Whereas SCAN also indicates that transfer of the *sat A* gene conferring resistance to virginiamycin occurs *in vitro* between isogenic strains of *Enterococcus faecium*; whereas virginiamycin-resistant *E. faecium* were detected in 22 % of food originating from pigs and in 54 % of that originating from poultry; whereas there are genetic factors for virginiamycin resistance existing within the human population, although it is not known how widespread they are; whereas two strains of *E. faecium* resistant to virginiamycin and pristinamycin, one isolated from a Dutch farmer and the other from his poultry, have the same genetic fingerprint; whereas even if general conclusions about the transfer of resistant enterococci from animals to humans should not be drawn from a single case, the Commission sees it as an indication that this might be confirmed by other cases in the future;
- (20) Whereas, after the SCAN opinion, Denmark produced major fresh evidence in August 1998 demonstrating a transfer *in vivo* under experimental conditions in the gastro-intestinal tract of rats of the *sat A* gene, via a plasmid, between isogenic strains of *E. faecium*;
- (21) Whereas, in the light of the foregoing, the Commission, for its part, takes the view that the risk of reducing the effectiveness of human medicinal products such as pristinamycin and the new combination dalfopristin/quinupristin, which is due to be authorised shortly as a human medicinal product, as a result of cross-resistance caused by virginiamycin should be avoided;
- (22) Whereas bacitracin zinc, a cyclic polypeptide, is also used in human medicine mainly for topical treatment of infections of the skin and mucosal surfaces; whereas publications show that it could possibly be used for the treatment of vancomycin resistant enterococci, which represent a clinical problem in human medicine; whereas selected resistances from the use of bacitracin zinc as a feed additive inevitably increase the reservoir of resistances to bacitracin zinc; whereas the percentage of *Enterococcus faecium* resistant to bacitracin zinc is higher in chickens which have received bacitracin zinc than in chickens which have not received it; whereas these resistances could be transferred from animals to humans and reduce the effectiveness of bacitracin zinc used as a human medicinal product; whereas the effectiveness of bacitracin zinc in human medicine should therefore be preserved;
- (23) Whereas according to the conclusions of the World Health Organisation conference held in Berlin in October 1997, the Economic and Social Committee of the European Union, the International Office of Epizootics and the conference on antibiotic resistance held in Copenhagen in September 1998, antibiotic resistance must henceforth be regarded as a major, complex problem of international dimensions; whereas, in the sense of the recommendations arising from these conferences, it is desirable to set up a system of general surveillance of antimicrobial resistance resulting from the use of antibiotics; whereas, furthermore, the phenomena of resistance encountered not only in hospitals but also in the general population should be addressed;
- (24) Whereas medicinal products belonging to new classes of antibiotics are not ready to be approved in the immediate future; whereas it is therefore imperative to preserve the effectiveness of those human medicinal products which are still effective;

- (25) Whereas one of the ways of achieving that aim, along with others relating to use of human medicinal products, is not to increase the reservoir of resistances in animals, especially where such resistances could be transferred to humans, thereby reducing the effectiveness of human medicinal products; whereas numerous scientific data demonstrate such a transfer not only for the organisms responsible for zoonoses but also for commensals;
- (26) Whereas one of the ways of preventing such a phenomenon, which originates in the use in livestock farming of antibiotics administered either as a veterinary medicinal product or as a feed additive, is no longer to authorise the use of antibiotics authorised as human medicinal products or known to select cross-resistance to antibiotics used in human medicine as additives, restricting the use of such substances for fundamental reasons to human medicine;
- (27) Whereas, for the sake of protecting human health, the authorisations for the antibiotics bacitracin zinc, spiramycin, virginiamycin and tylosin phosphate should be withdrawn;
- (28) Whereas, on the basis of current scientific and technical knowledge, it would appear, however, that the evidence presented by the Kingdom of Sweden does not justify withdrawal of the authorisations for the antibiotics monensin sodium and salinomycin sodium, of the ionophore group, since no ionophore is to date used in veterinary or human medicine and the two substances, in the current state of knowledge, do not select cross-resistance to antibiotics used in human or veterinary medicine;
- (29) Whereas the prohibition on the use of the antibiotics bacitracin zinc, spiramycin, virginiamycin and tylosin phosphate ought to be perceived as an interim protective measure taken as a precaution, which could be reconsidered in the light of the investigations which will have been carried out and of the established surveillance programme;
- (30) Whereas, on the basis of current scientific and technical knowledge, it would also appear that the evidence presented by the Kingdom of Sweden does not justify a ban on the antibiotic flavophospholipol of the phosphoglycopeptide group since no substance belonging to the same group is to date used in veterinary or human medicine and flavophospholipol, in the current state of knowledge, does not select cross-resistance to antibiotics used in human or veterinary medicine;
- (31) Whereas, on the basis of current scientific and technical knowledge it would appear that the evidence presented by the Kingdom of Sweden does not justify a ban on the antibiotic avilamycin, belonging to the group of orthosomycins, since no substance belonging to that group is to date used in human medicine; whereas that decision will be reviewed in the light of additional studies to be supplied by the person responsible for the entry into circulation of avilamycin, concerning the mechanisms of resistance, the development of resistance in certain micro-organisms and in particular *Enterococcus faecium*, and any cross-resistance to everninomycin, which is currently under development with a view to future approval for use in human medicine or to other substances used in human medicine having the same site of action as avilamycin;
- (32) Whereas the maintenance of the authorisations for monensin sodium, salinomycin sodium, flavophospholipol and avilamycin will have to be reviewed in the light of the results of the work on antimicrobial resistance carried out by the working group set up by the Scientific Steering Committee;
- (33) Whereas after 31 December 1998 the Kingdom of Sweden is required to apply the Community legislation on feed additives in its entirety;
- (34) Whereas a transitional period to comply with the provisions of this Regulation is necessary in the Member States where one or more of the additives referred to in Article 1 are authorised at present;
- (35) Whereas, in the absence of an opinion of the Standing Committee on Feedingstuffs, the Commission has been unable to adopt the provisions it envisaged under the procedures laid down in Articles 23 and 24 of Directive 70/524/EEC,

HAS ADOPTED THIS REGULATION:

#### Article 1

The entries in Annex B to Directive 70/524/EEC for the following antibiotics shall be deleted:

- bacitracin zinc,
- spiramycin,
- virginiamycin,
- tylosin phosphate.

*Article 2*

The Commission shall reexamine the provisions of this Regulation before 31 December 2000 on the basis of the results given by

- the different investigations concerning the induction of resistances by the use of the antibiotics concerned, and
- the surveillance programme of microbial resistance in animals which have received antibiotics, to be carried out in particular by the persons responsible for putting the additives concerned into circulation.

*Article 3*

This Regulation shall enter into force on the day of its publication in the *Official Journal of the European Communities*.

It shall apply from 1 January 1999.

However, where, on the date on which this Regulation enters into force, a Member State has not banned, in accordance with Community law, one or more of the antibiotics referred to in Article 1 of this Regulation, such antibiotic or antibiotics shall remain authorised in that Member State until 30 June 1999.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 17 December 1998.

*For the Council*

*The President*

W. MOLTERER

---