Brussels, 30 June 7 July 1998

DRAFT OPINION

of the

Section for Protection of the Environment, Public Health and Consumer Affairs on the

Resistance to antibiotics as a threat to public health

(own-initiative opinion) Rapporteur: **Mrs Ström**

N.B. This document will be discussed at the Section meeting on **7 July 1998**

On 27 January 1998 the Economic and Social Committee decided, under Rule 23(3) of its Rules of Procedure, to draw up an Own-initiative Opinion on *Resistance to antibiotics as a threat to public health.*

The Section for Protection of the Environment, Public Health and Consumer Affairs, which was responsible for preparing the Committee's work on the subject, adopted its opinion on 7 July 1998.... The rapporteur was **Mrs Ström**.

At its plenary session the Committee adopted the following opinion:

1. Introduction

1. This own-initiative opinion aims to explore the problem of antibiotic resistance, a problem that constitutes an increasing threat to public health. Infections caused by resistant bacteria contribute to morbidity and mortality resulting in additional health and medical care costs. That the seriousness of this problem is increasingly recognized is shown by numerous recent initiatives both at the level of the Member States (including a 1998 report by the British House of Lords and an international Conference to be organised by the Danish Government in September 1998), within the EU (e.g. the recent decision by the Scientific Steering Committee acting on request of the Commission to establish an ad hoc multidisciplinary working group with the mandate to examine the issue in all its various aspects) and in international fora (the activities of the WHO Antimicrobial Resistance Monitoring programme as well as the Resolution recently adopted by the World Health Assembly).
2. In order to make a contribution to this discussion and also against the background of the debate on the recent Commission communication on the future of public health policy in the European Community, this opinion indicates various ways of tackling the problem of antibiotic resistance. It first sketches the background to the problem and gives examples of existing initiatives at different levels (national, EU, international), such as antibiotic resistance surveillance systems. Subsequently, it makes a number of recommendations for future action at national and EU level, stressing that the proposed measures should best be taken as part of a comprehensive and integrated policy.
3. Though the drive to curb the emergent resistance problem must take account of human healthcare, veterinary medicine and animal husbandry, as parts of the same eco-system, the opinion will mainly focus on the resistance problem in health and medical care and patterns of antibiotics consumption in human medicine. It is based on the assumption that combating the problem requires the combined and coordinated effort of all the actors involved: the general

public, authorities, physicians, patients, veterinarians, industry, researchers, consumers, farmers, etc..

4. Although resistant bacteria were found shortly after the introduction of penicillin into clinical practice, it is not until only in recent years that this problem has started to attract broad public attention. This is because the pharmaceutical industry has until recently succeeded in developing new antibiotics when resistance to existing ones emerged. However, bacteria now accumulate several different resistances, making it increasingly difficult to develop new drugs. The prevalence of antibiotic-resistant bacteria is now rising and it is sometimes difficult to find effective treatment against bacterial diseases. Although there is an ongoing research to find targets for new drugs to combat resistant bacteria, it is uncertain when such drugs will eventually be available. It is therefore of utmost importance that the antibiotics that still work are used rationally and with caution. In addition, research on the optimal use of specific antibiotics as well as on other risk factors for resistance should be given high priority.

2. BACKGROUND INFORMATION

1. History

For billions of years the presence of antibiotics in nature has been of the utmost importance for the delicate balance between micro-organisms on earth. Antibiotics have probably also been used as therapeutic agents for centuries before their discovery by modern science. Traces of tetracycline have been found in 1,000-year-old Nubian mummies and some scientists believe that the long survival of the Nubian culture may in part be due to the presence and use of antibiotics. Modern scientific bacteriology was introduced in the late nineteenth century and the discovery of penicillin in 1928 by Sir Alexander Fleming is usually considered to be the beginning of the modern antibiotic era. To conceive the amazing impact on human health of the introduction of antibiotic treatment, one must realize that hospital wards in the 1930s were crowded by patients with pneumonia, meningitis, bacteremia, typhoid fever, rheumatic fever, syphilis, tuberculosis and wound infections. There were few effective methods of treating these conditions. The introduction of antibacterial agents had a tremendous impact on the morbidity and mortality of infectious diseases and has without any doubt been one of the twentieth century's foremost successes in medicine. Already in 1944, shortly after the discovery of penicillin, Fleming noted that some strains of Staphylococcus aureus were capable of destroying penicillin and warned that the misuse of penicillin could lead to the selection of genetic mutations in bacteria, which thereby became resistant to the drug. Now, after a half-century of antibiotic use, antibiotic resistance genes are more or less prevalent in virtually all the major bacterial pathogens. This development is rapidly becoming a major threat to public health on a global basis. Tuberculosis bacteria, multi-resistant to antibiotics, are re-emerging as the leading cause of death in the world. Today, hospital in-patients are suffering from infections caused by enterococci resistant to most antibiotics, leading to high mortality rates. In some parts of the world, including Europe, children sometimes have to be treated with powerful antibiotics for common middle ear infections, due to the spread of recently imported resistant strains of pneumococci. In the developing countries, multi-resistant strains of bacteria, causing dysentery lead to high mortality due to

lack of funds to purchase the few (expensive) modern antibiotics left to treat these infections.

2. What is antibiotic resistance?

Bacteria exhibit genetic diversity and flexibility. When they divide and increase in number, random changes (mutations) can occur in their genetic make-up which may trigger antibiotic resistance. The bacterial cell wall may for instance undergo changes impeding the antibiotic molecules to enter into the bacterial cell or the bacteria may acquire enzymes that can destroy the antibiotic. Bacteria may also become antibiotic-resistant by acquiring genetic elements that can be transferred from other resistant bacteria. Such transfer of bacterial genes is also possible between bacteria belonging to different bacterial species. Studies of bacterial genetics have shown that resistance genes often consist of mobile elements which confer simultaneous resistance to many antibiotics. Antibiotic resistance should therefore be looked upon as a phenomenon of genetic ecology. A very large number of bacteria, which we call the normal bacterial flora, are carried by human beings and animals, e.g. on the skin, in the mucous membrane and in the gut, where they are necessary for certain key bodily functions. Such bacteria will be influenced by treatment with antibiotics which may then select for resistant bacteria in the normal flora. Since most bacteria divide within very short time-spans resistance can then spread quickly.

3. How widespread is antibiotic resistance?

Today there is grave, world-wide concern among health authorities, physicians, veterinarians and researchers working in the field of infectious diseases that rapidly emerging antibiotic resistance will significantly reduce our possibilities of treating common infectious diseases. Although efforts are made to reduce the spread of antibiotic resistance, the problem is still increasing. Bacteria and bacterial genes can transfer freely between various ecological systems (e.g. from person to person in and outside hospitals, from animal to food or from food to person), meaning that wherever bacteria spread, resistance may also spread. However, recent reports from several countries indicate that, provided appropriate action is taken, there might still be time to contain the further emergence and spread of resistant bacteria.

1. *The community context*

Pneumonia caused by pneumococci is among the most common community-acquired infections around the world; the most affected are the elderly and young children. Another common disease caused by this bacterium is middle-ear infection (otitis media). Pneumococcal penicillin resistance is now prevalent in many countries. In Europe, the highest resistance levels are found in France and Spain (35%-50%). Hence these common infections are increasingly difficult to treat and in some cases require high doses of antibiotics which can only be given by injections, thereby pushing up healthcare costs.

Tuberculosis (TB) bacteria multi-resistant to antibiotics are a major problem in the developing countries but also in Europe and elsewhere in the industrialized world. Outbreaks of multi-resistant TB have been reported in 35 states in the USA as well as in many European countries.

The world-wide spread of TB has been facilitated by the HIV epidemic, since patients with lowered immune defences succumb more easily to such difficult-to-treat infections.

2. *The food chain*

The incidence of human salmonella infections has increased considerably in many European countries during the last decades. Salmonella originating from colonised cattle, chicken or eggs can be transmitted via the food chain. Occasionally, salmonella infections can cause bacterial invasion of tissues and the bloodstream, and then effective antibiotic treatment is needed. In many European countries some strains of salmonella bacteria have become increasingly insensitive to antibiotics on account of the alarming spread of multiple antibiotic resistance. Campylobacter, another gut bacterium transmitted via the food chain, is now showing increasing signs of resistance to certain antibiotics.

3. *The hospital setting*

Bacteria causing hospital infections have become more and more prevalent. Here staphylococci are still the single most common bacterium but many other bacterial strains have started to emerge as important causes of hospital infections. The spread of Methicillin-resistant staphylococci (MRSA), which are often resistant to multiple antibiotics, illustrates the present health care problem of difficult-to-treat infections. Prevalence of MRSA in Europe varies considerably from country to country. In 1992, an extensive survey covering over 10,000 patients in more than 1,400 intensive care units in 17 countries in Western Europe found that on average 60% of all staphylococci were MRSA.

Other bacteria which can cause hospital infections are the enterococci. These are intrinsically resistant to many antibiotics and frequently only one antibiotic group (glycopeptides) has been available for treatment purposes. Now glycopeptide-resistant enterococci are spreading in health care facilities in many countries, ruling out effective treatment. Examples like these justify the fear of a post-antibiotics era. As enterococci are part of the normal bowel flora of humans, they are almost impossible to dislodge. A horizontal genetic transfer of vancomycin resistance to staphylococci seems to be merely a matter of time and there is increasing fear in the health care system that this threat will become a reality, as well as ofover the serious treatment problems which can then be expected.

4. Factors underlying the development and spread of antibiotic resistance

The changes in the bacterial genetic make-up (e.g. chromosome mutations) underlying the development of antibiotic resistance occur all the time, regardless of whether the micro-organism is exposed to antibiotics or not. A key factor for the propagation of a bacterium with acquired antibiotic resistance is whether antibiotics capable of curbing or killing off the normal (antibiotic sensitive) bacteria exist in the environment, thereby providing "space" for resistant organisms to flourish and expand. This is known as selective antibiotic pressure.

In all ecological systems where antibiotics are used, two major factors influence the magnitude of the antibiotic resistance problem. Today there is

international consensus among physicians and researchers that inappropriate antibiotic usage is one of the key factors responsible for a major contributor to the emergence of antibiotic resistance. Numerous surveys and studies support this causal relationship,,,. The other key factor is Besides antibiotic usage, other key factors are the resistant bacterium's possibilities and capacity for propagation in the environment such as and environmental conditions which favour person to person spread.

1. *The community*

The emergence and spread of resistant bacteria in the community of today has several different explanations:

- Many factors can cause the inappropriate use misuse of antibiotics, thereby also influencing the development of resistance:
- the largest quantities of antibiotics are used for the treatment of respiratory tract infections, the majority of which are caused by viruses and not treatable with antibiotics. Only limited tools are available to most physicians in order to determine whether an infection is caused by virus or bacteria. In case of doubt, where the physician is face to face with an ill patient, fear of overlooking a bacterial infection or concern about malpractice lawsuit may result in a prescription "for safety's sake";
- strong demands or expectations on the part of patients or parents regarding antibiotic prescription for treatment of infections that are often not of bacterial origin (e.g. colds or viral respiratory infections);
- low level of awareness among both physicians and patients of the resistance risks associated with inappropriate use of these drugs;
- the possibility, in some countries, to purchase antibiotics "over the counter" without a prescription;
- suboptimal antibiotic regimens e.g. inappropriate doses and/or treatment times;
- the sale of counterfeit antibiotic preparations in some countries, notably the developing countries. The use of such products containing none, not enough or different active substances can lead to "under-treatment", thereby inducing resistance.
- Poor socio-economic conditions in countries where poverty and overcrowding are rife encourages the emergence and propagation of resistant bacteria.
- In the industrialized countries too, social factors influence the spread of resistance. These include "close contact" environments such as nursing establishments, schools and day nurseries. In Iceland, the high proportion of children frequenting day-care centres has been regarded as a significant cause of the rapid spread, for instance, of penicillin-resistant pneumococci in that country.
- Increased travel enables the rapid transmission of drug-resistant organisms.
- Globalization of food supply creates conditions conducive to the fast spread of bacteria transmitted via the food chain.

1. *The hospital setting*

- Use of broad-spectrum antibiotics is often a necessity in healthcare since the patients who today receive treatment therapy are often affected by serious bacterial infections, for instance in connection with treatment that reduces their defences (cytostatic drugs, transplantations). Such antibiotic treatment facilitates selection of resistant bacteria.

- The use of complicated technical equipment within health care provides "niches" for new bacteria that otherwise would not thrive. Assisted ventilation devices, dialysis equipment and catheter use are some examples.
- Hygiene and proper isolation facilities in hospitals are of the utmost importance to avoid the spread of resistant strains of bacteria.

1. *Veterinary medicine and animal husbandry*
   Antibiotic use in animals takes both place in the form of feed additives for growth promotion purposes in animal husbandry and as veterinary medicine for purposes of curative treatment and disease prevention. Some countries report that more than 50 percent of their total output of antimicrobial compounds is used in agriculture (i.e. livestock, fish and plant production); most are applied to food animals as growth promoters. In some countries, the quantity of antibiotics used for non-human purposes, much of which is used for growth promotion, outstrips their use in human medicine. Administration of antibiotics to animals may select for antibiotic resistant bacteria in the animal population which may then spread to humans via the food chain. Some of these bacteria, such as salmonella and campylobacter, may be a direct cause of severe human diseases via the food chain. At a WHO meeting with experts in this field, in October 1997, it was highlighted that "(t)here is direct evidence that antimicrobial use in animals selects for antimicrobial-resistant nontyphoid s*almonella* serotypes" and that "(t)hese bacteria have been transmitted to humans in food or through direct contact with animals." Evidence was also presented that the use of feed additives has contributed to the reservoir of resistance genes to glycopeptides in enterococci. Further, the group of experts considered that attention must be given to the risks associated with widespread use of fluoroquinolones as medicines for animals, especially as these drugs are an important group of antibiotics in human medicine. To this end, a WHO meeting was held in June 1998 on "The Use of Quinolones in Food Animals and Potential Impact on Human Health".

2. *Agriculture*

Antibiotics are also used in large amounts in agriculture for prevention of bacterial diseases in plants as well as for crop protection and wood conservation. Figures are not readily available. As an example it can be noted that in the US at least 10,000 kg of streptomycin are used annually for the control of fire blight in apples and pears. Streptomycin and tetracyclines are also used increasingly against bacterial spot in tomatoes and peppers and soft rot in potatoes. In the EU more than 800 substances are licensed for plant protection, a number of which are antibiotics.

1. **Financial impact of antibiotic resistance on health care**
   The cost for the individual patient infected with antibiotic resistant bacteria, in terms of prolonged hospitalization, suffering, failed operations and possibly death in an untreatable infection, is obvious. Trying to estimate the cost for society as a whole of the increasing prevalence of antibiotic resistance is difficult. A review by Holmberg and others concludes that "although the adverse economic and health effects of drug-resistant bacterial infections can only roughly be quantified, (…) antimicrobial resistance is an important health

problem and an economic burden to society." A case in point is that the US Centres for Disease Control and Prevention (CDC) recently estimated the direct medical costs of one patient with a blood-stream infection caused by vancomycin-resistant enterococci at US$ 18,000/hospitalization. Comparable figures for Europe are very scarce; as an indication it could be noted that if a difficult to treat antibiotic infection required one week in intensive care, this would in some Member States amount to at least US$ 12,000.

2. Is antibiotic resistance reversible?

It is often assumed that the carriage of antibiotic resistance genes implies a "burden" for bacteria, which among other things causes them to grow more slowly than normal bacteria. This assumption is also the basis for the rational conclusion that reduced antibiotic consumption can help curb the emergence of resistant bacteria in the community, as they will then be outcompeted by the "reappearing" normal bacteria. Some recent examples can be given supporting the assumption that changes in antibiotic consumption can contain the emergence of a certain type of antibiotic resistance at national/local level. However, new genetic studies have shown that resistant bacteria may incorporate additional genes which will compensate for the "burden" that resistance causes, thus making the resistant bacteria as competitive as normal ones. More must speedily be learned about the molecular and genetic phenomena underlying the development of antibiotic resistance.

1. EXISTING INITIATIVES TO COMBAT ANTIBIOTIC RESISTANCE AT DIFFERENT LEVELS

1. Introduction

1. Below, an overview will be given of a number of existing initiatives to combat the problem of antibiotic resistance - both at national, EU and international level. This will be founded in partly done on the basis of the answers to four thematic questionnaires sent out to relevant contact persons in the Member States (as well as Hungary and the Czech Republic) in the beginning of April 1998 (see Appendix I). Without aimingpretending to give an exhaustive picture of the situation in the Member States, the information obtained through these questionnaires does highlight a number of areas for further analysis and discussion.

2. Existing initiatives to fight antibiotic resistance - which in some countries such as Denmark and Sweden are part of an integrated strategy - as well as recommendations for future action (see part 4 below) can be described in the following broad categories:

- antibiotic usage in humans, and animals and in plant protection: elements of good practice;
- monitoring antibiotic usage;
- surveillance of antibiotic resistance among bacteria isolated from humans and animals;
- infection control in hospital and non-hospital care;
- research;
- education and other measures.

1. **Antibiotic usage in humans and animals: elements of good practice**
    1. Major importance should be attached to measures to promote behavioural changes of all the actors involved with a view to stimulating encouraging a wiser use of antibiotics. Such measures include the drawing-up of guidelines for doctors and patients as well as for veterinarians and their clients on when and how to prescribe/to use antibiotics; a review of rules about who is authorised to prescribe and sell antibiotics; an assessment of reimbursement systems; educational materials for the actors involved about on the nature of the resistance problems and ways to tackle it and so onetc.

    2. *Antibiotic usage in humans*
        1. As to the rules governing antibiotic usage at **Member State level,** the following conclusions can be drawn from the replies the response to the questionnaires on "Availability and Consumption of Antimicrobial Agents in Human Medicine" and on "Guidelines and Educational Activities on the Use of Antimicrobial Agents" (see Appendix I) allows for the following conclusions:

- In all the Member States for which information has been receivedthat have responded a doctor's prescription is needed for oral and parenteral antibiotics; in none of these countries can prescribed antibiotics be obtained other than from doctors, hospitals or licensed pharmacists. In addition, in all of these countries prescribed antibiotics are covered by a reimbursement system.;
- In many Member States national guidelines on antibiotic treatment policies (either of a general nature and/or on specific indications) have been drawn up. In a few countries (Italy, Luxembourg, Portugal) no such guidelines appear to exist to date; in the Netherlands first attempts to agree on such national guidelines have just been made.
- Where such guidelines exist, compliance is monitored in a number of cases, whereas in other countries (e.g. UK, Germany, France) this has not been done so far.
- Refresher courses (in oral and/or written form) for physicians on the use of antibiotics are arranged in a number of Member States, whereas in other countries (Portugal, the United Kingdom) such courses have not been systematically organised so far.

        1. As regards activities at **EU level**, reference can inter alia be made to the request made by the European Agency for the Evaluation of Medicinal Products (EMEA) to the Member States to inform the EMEA's Committee for Proprietary Medicinal Products (CPMP) about any existing official guidelines on the rational use of antibiotics.

    1. *Antibiotic usage in animals*
        1. Here a distinction should be made between the use of antibiotics as **veterinary medicine** on the one hand and as **growth promoters in animal feed** on the other. Recent discussions in the Community have very much focussed on the latter.

        2. Currently around ten different antibacterial agents are recognized as growth promotion substances in the EU. However, some Member States have restricted the use of such

growth promoters either through legislation or by means of voluntary instruments. The only Member State which has banned the use of antibiotics as feed additives for growth promotion purposes is Sweden (the ban has been in force since l986). On Sweden's accession to the European Union, it was agreed that up to 31 December 1998, it would be authorised to retain its general ban on the use of antibiotics as feed additives. In addition, Finland was granted exemptions relating to the use of *certain* antibiotics for growth promotion purposes (applying until the end of 1997).

3. Avoparcin, previously used for growth promoting purposes, is very closely related to vancomycin, which is one of the major antibiotic preparations in human health care. The use of avoparcin in animal husbandry is criticized since it may select vancomycin resistance genes that can spread, e.g. via the food chain. In May 1995 and January 1996 respectively, Denmark and Germany, invoking the safeguard clause contained in Article 11 of Directive 70/524/EEC, unilaterally prohibited the use on their territories of avoparcin in animal feeding stuffs. Consequently, in January 1997, the European Commission, acting on the basis of the precautionary principle, suspended the authorisation to use avoparcin in animals pending an investigation of the possible risks involved (Directive 97/6/EC of 30 January 1997 amending Council Directive 70/524/EEC concerning additives in feedings).

3.2.3.4 It should be noted, however, that other antibiotics are also used as growth promoters in animal husbandry. For certain of these antibiotics (e.g. avilamycin, spiramycin, tylosin, virginiamycin), similar substances are also used in (or being developed for) human medicine. Unfortunately, there are already indications of the development of resistance to these antibiotics, which can mean that their effective timespan for the purpose of human medicine is reduced. It is on this basis that the safeguard clause of Directive 70/524/EEC has recently been invoked by Finland (for tylosin and spiramycin) and Denmark (for virginamycin).

1. **Monitoring antibiotic usage**
    1. The existence of monitoring systems and statistics regarding antibiotic usage/sales is of key importance, as it can provide valuable information on the correlation between usage levels and resistance patterns.
    2. *Monitoring antibiotic usage in human medicine*

ConcerningAs regards the monitoring of antibiotic usage in humans in the **Member States,** the following conclusions can be drawn from the response got so far to the questionnaire on "Availability and Consumption of Antimicrobial Agents in Human Medicine": allows for the following conclusions:

- Official statistics on the quantities of antibiotics prescribed/sold are available in a number of Member States; in a number of cases such statistics only cover part of the antibiotic consumption (e.g. because usage in hospitals or usage not reimbursed by the

national health service are not monitored). For a number of countries (Italy, France, the Netherlands) respondents indicate that such official statistics are not normally available.

- As regards the level to which official statistics can be broken down (national, regional, local, hospital, individual prescribers) the situation appears to vary greatly between Member States. Only for two countries are data said to be available at all of the levels cited (Portugal and Finland; in this latter country statistics on local, hospital and prescriber level are only available for administrative and research purposes).

1. Monitoring antibiotic usage in animals

With a few exceptions (e.g. Denmark and Sweden) useful data on antibiotic usage in animals are not readily available in the EU Member States. It should be noted, however, that as from 1 April 1998, Directive 95/69/EEC requires establishments manufacturing antibiotics used as additives in feedingstuffs to hold a register to ensure the tractability of the quantities of antibiotics used, specifying amongst other things the nature and the quantity of the additive bought. This register is at the disposal of the competent authorities of the Member States. In addition, any person permitted to sell veterinary medicinal products in retail is required to keep detailed records of different aspects of incoming and outcoming transactions.

1. **Surveillance of antibiotic resistance among bacteria isolated from humans and animals**
    1. To provide the necessary basis for changing prescription and usage patterns and for taking other action to combat antibiotic resistance, comprehensive and permanent surveillance systems are indispensable. In recent years, several initiatives have been launched to establish or strengthen surveillance systems, both in the Member States and at EU/international level. Whilst as such this is a positive development as such, the question should be examined of whether there is a need for additional action and/or for increased coordination between existing initiatives should be examined. Common problems include the fact that in a number of cases existing local surveillance systems do not feed their data into a national system;, the comparability of data;, the fact that data are not broadly accessible;, missing links between laboratory and clinical data;, etc.
    2. As part of the WHO Antimicrobial Resistance Monitoring programme (see for a short description Appendix III) an overview of **national activities** in antimicrobial resistance surveillance was presented at a meeting that took place in December 1997 in Verona.

        1. Turning to the information obtained through the questionnaire on the "Surveillance of Antibiotic Resistance" (see Appendix I), it can be concluded that:

- In the majority of the countries about which information has been received, there is some sort of system at national level for the voluntary or mandatory reporting of selected bacterial pathogens resistant to certain antibiotics in human health care. There are, however, large differences in coverage: whereas in some countries (e.g. the Czech Republic, Italy, Hungary, the Netherlands and Sweden) a large number of relevant pathogens (including MRSA, VRE, PC resistant Pneumococci and Multiresistant Gram-negative) are covered, in other countries antibiotic resistance monitoring

activities have a more limited scope. In most of these countries (except for the UK and Italy) this information is made officially available. In some Member States (Germany, Ireland, Luxembourg, Portugal and Spain) no national reporting system exists at present.

- In most of the Member States there are national quality assurance programmes for antimicrobial susceptibility testing; in all but two of these cases (Denmark and Spain) they also cover private laboratories. In Austria, Ireland, Italy and Portugal no such national programme exists; in Austria, Ireland and Portugal a number of labs use the National External Quality Assurance Scheme operated by the PHLS of England and Wales.

1. There are many recent examples of As far as **initiatives at European and international level** are concerned recent examples are numerous.

    1. Special mention should be made of recently launched EARSS project that aims at setting up a European Antimicrobial Resistance Surveillance System (see Appendix IV) as well as of the Global Information Bank that is under development as part of the WHO Antimicrobial Resistance Monitoring programme (see Appendix III). A number of other EU funded projects such as the Tuberculosis Surveillance Network, the project on Nosocomial Infections co-ordinated by EZUS in Lyon and the Salmnet/Enternet project also include action regarding antibiotic resistance surveillance (see Appendix IV).
    2. In this context, the relevance of the activities of EMEA should also be highlighted. This applies in particular to the "Note for Guidance on the Pharmacodynamic Section of the Summary of Product Characteristics (SPC) for Anti-Bacterial Medicinal Products" recently approved by the CPMP. This document addressed to industry and to regulatory authorities gives guidance on how to provide product information to health care professionals and patients before introducing a new antibiotic. Recognising the problem of geographic differences in occurrence of resistance in the EU, the document requires "Marketing Authorisation Holders" to provide and update information on local resistance patterns. This information, which furnishes clinicians with relevant information when prescribing these products to treat infections, is then incorporated into the section on pharmacodynamic properties in the SPC and is also included in the European Public Assessment Reports.

2. As regards the **surveillance of antibiotic resistance in animals**, mention can *inter alia* be made of the activities undertaken by EMEA's Committee for Veterinary Medicinal Products (CVMP) that is currently examining the occurrence of antibiotic resistance in animals as well as its possible transfer to man. In addition, reference should also be made to the surveillance programme set up in response to Article 2 of Directive 97/6/EC (see 3.1.3.2 3.2.3.3). As a first step, this programme, which might be extended in future, is be limited to one organism (*Enterococcus faecium*), while focussing on a selected number of Feed

Additive Antibacterial compounds and Member States (some further details on this "first protocol" are given in Appendix IV).

1. **Infection control in hospitals and non-hospital care**
    1. Currently, several initiatives are being undertaken to obtain an overview of strategies to combat infections in the Member States. Initiatives include the ESCMID Study group on Hospital Infections, the HELICS European Group on Nosocomial Infections and the project on Nosocomial Infections co-ordinated by EZUS in Lyon.
    2. The following may be concluded from the replies answers received to the questionnaire on "Infection Control Policy" (see Appendix I) allow for the following conclusions:

- In a large number of Member States national guidelines have been published on infection control policies in hospital and non-hospital care. In Finland a nationwide hospital infection control policy is still in a pilot phase; in Hungary it is currently being drawn upunder elaboration. In Austria national infection control guidelines do not exist at present.
- In most of the countries in questionMember States (with the exception of Hungary and Luxembourg) the implementation of infection control programmes is mandatory in hospitals.
- Whereas in a number of countries formal infection control training programmes are provided for both for physicians and for nurses, in some other Member States (e.g. Luxembourg, Spain and Sweden), such training programmes do not exist.

1. **Research**
    1. Both within academia and the pharmaceutical industry research in the field of antibiotic resistance is given increased attention. Research activities include projects aiming at a better understanding of the mechanism behind the emergence of antibiotic resistance as well as the development of new techniques to find molecular targets for new antibiotics.
    2. On the European scientific and technological research front, medical research in this field is of particular importance in the context of both the EU multiannual research programmes and of the EUREKA and COST initiatives. The JRC and Ispra play an active role in the EU's direct research work.
    3. Under the 3rd and 4th Community RTD framework programmes, major specific programmes (BIOMED 1 and 2) have focused on research in this sector. In the context of the Fourth Framework Programme reference should also be made to the FAIR programme on research in the field of agriculture and fisheries, as this has financed a number of research projects related to antibiotic resistance in bacteria from animals. It should furthermore be noted that the proposals for the 5th framework programme (1998-2002), on which the Committee is currently preparing an opinion, provide for specific actions to control infectious diseases, with strategies based on treatment and prevention as well as on studies of resistance pathogenesis and the monitoring of Community responses. Other key actions under the 5th framework programme include research into health-related innovative products and

processes, with particular reference to molecular engineering for antibiotic preparations, for both human and animal use.

1. RECOMMENDATIONS FOR FUTURE ACTION AT NATIONAL AND EU LEVEL

1. Introduction

Taking account of existing activities and structures as described in part 3 of this opinion and the appendixces, the Committee proposes a number of makes the following recommendations for future action to fight antibiotic resistance, both at national and - where relevant and feasible - EU level (see below points 4.2-4.7). Given the multi-disciplinary nature of the problem it is essential that the proposed measures are taken as part of an all-embracing, integrated policy to be co-ordinated by a central body. Hitherto, the different aspects of the resistance problem have too often been addressed separately. Against this background, initiatives like the Danish DANMAP and Swedish STRAMA programme (see 3.1 above) as well as the recent decision by the Scientific Steering Committee to examine the question of antibiotic resistance from all angles, must be judged positively.

2. Antibiotic usage in humans and animals: elements of good practice

- The Commission should encourage and support the framing of guidelines in all Member States for rational antibiotic use within human and veterinary medicine. These guidelines should be regularly updated on the basis of new scientific information and clinical experience and need to be tailored according to local antibiotic policies and resistance patterns. Although such guidelines have to be considered as recommendations and decision supporting instruments rather than strict regulations which would possibly restrict therapeutic intervention by the physician, it is important that the degree of adherence to the guidelines is monitored at regular intervals.
- The rational use of antibiotics will best be ensured if over-the-counter sales of antibiotics is avoided. Therefore, trends to deregulate the supply of antibiotics by modifying their status as "prescription-only medicines" should be opposed. In other words, prescription needs to remain in the hands of physicians and veterinarians.
- In the animal field, the use of antibiotics should be limited to (well established) veterinary medical purposes. In this connection, the Committee shares the view expressed by the Expert Committee at the October 1997 WHO meeting in Berlin that "(i)ncreased concerns regarding risks to public health resulting from use of antimicrobial growth promoters indicate that it is essential to have a systematic approach towards replacing growth promoting antimicrobials with safer, non-antimicrobial alternatives". In this context, the emphasis should be first and foremost on limiting the use of antibiotics that can provoke cross-resistance to drugs that are or will become relevant in human health care.

1. Monitoring antibiotic usage

- An ongoing review of the volumes and patterns of usage of antibiotics at national and European level is essential; hence structures should be set up at the level of each Member State responsible for charged with collecting and analysing relevant information. Such monitoring schemes should cover the amounts and types of antibiotics used in humans (both hospital and non-hospital care), animals as well as for

plant protection purposes. To be meaningful for comparison, data collection in the Member States should be harmonised in terms of classification systems of different antibiotics and as regards the units used for measuring usage volumes. Efforts must be made to collect statistics as close to grassroots level as possible. In this connection, a system of regular (i.e. at least annual) reporting should also be provided for.

- In addition to national structures, a European focal point needs to be established for the co-ordination and exchange of information coming from the Member States.

1. **Surveillance of antibiotic resistance among bacteria isolated from humans and animals**

- To monitor and analyse the national and European antibiotic resistance situation, appropriate antibiotic surveillance systems should be set up at national level, similar to the structures proposed above for the monitoring of antibiotic usage. Such systems should also encompass data on resistance in bacteria isolated from animals. Resistance to antibiotics should not only be monitored in pathogenic and zoonotic bacteria, but also in indicator bacteria. The joint surveillance of resistance patterns in humans and animals can pave the way for greater understanding of the interaction between ecological systems and establish a platform for research cooperation. This system must be able to provide an accurate picture of the national problem and, for purposes of comparison, cover external quality assurance of detection methods. In the development of a national surveillance system, initial efforts in human health care could for instance be focussed on the prevalence of MRSA, VRE, penicillin-resistant pneumococci and multiresistant Gram-negative bacteria in blood cultures. The Member States should report on developments in antibiotic resistance at least once a year. The proposed surveillance systems will require considerable resources from the Member States and the EU. In addition, the functioning of the system will entail substantial costs for industry that will have to provide surveillance data.
- In addition to national surveillance systems, a focal point at European level needs to be established, inter alia to collect and analyse the information coming from the Member States and to ensure full comparability of national data. In this context the possible relevance of the proposed "Network for the epidemiological surveillance and control of communicable diseases in the European Community" as well as of the possible future establishment of similar networks covering other subject matters should be further examined.

1. **Infection control in hospital and non-hospital care**

- Every Member State should develop nationally standardised infection control guidelines and, where these already exist, review them, as a measure to minimize the spread of antibiotic resistant bacteria in hospital as well as non-hospital care. In this connection, systems for quality control including local follow-up of resistance patterns, antimicrobial usage and educational activities should also be considered. Infection control programmes including trained infection control teams should be a central part of good hospital management and should be given sufficient resources.

1. **Research**

There is an urgent need for a better understanding of the risk factors involved in the emergence and spread of antibiotic resistance. Priority must be given to research efforts on:

- estimating the risk for specific antibiotics to lose their effectiveness as a result of resistance development, by carrying out quantitative studies of the evolution of

antibiotic resistance within a bacterial population and by improving the design of clinical trials;

- improving our understanding of the transmissibility of resistant bacteria in different ecological niches e.g. in patients (hospitalised and non-hospitalised), in different animal populations and in the environment;
- the impact of antibiotic usage practices for the development of antibiotic resistance in the Member States;
- optimizing antibiotic dosage (dose, duration of treatment) to reduce the risk of developing resistance;
- the development of new diagnostic technology enabling general practitioners to easily and quickly identify quickly and easily the causative pathogen as well as susceptibility testing systems;
- the development of effective bacterial vaccines.

Obviously the EU Research Framework Programmes can play a crucial role in this field. It is therefore of utmost importance that R&D activities on antibiotic resistance are incorporated in the 5th Framework Programme (1998-2002), which is presently being discussed between the Institutions.

1. Education and other measures

- A single body in the EU (the EMEA - including the European Economic Area and involving the Central and Eastern European countries) should become responsible for applications for marketing authorisations of antibiotics for human and veterinary use. To this end, the scope of the "centralised procedure" should be extended.
- Permanent and strict co-ordination should be ensured between the different bodies responsible for the evaluation and supervision of antibiotics used in human and veterinary medicine (currently the EMEA and national authorities) as well as for purposes of animal growth promotion and plant protection. To this end, the establishment of a single data base for the collection of relevant information should also be considered. The question should also be addressed as to whether, when evaluating antibiotics, sufficient account is taken of any undesirable effects they may have on the normal bacterial flora.
- As regards pharmacovigilance once medicinal products have been authorised, antibiotic resistance should be considered an indirect adverse effect of antibiotics and its the surveillance of resistance patterns should be regarded as a particular aspect of the surveillance of 'non-efficacy'. In this light, the recent extension of the scope of the so-called 'Adverse Drug Reaction Reports' for veterinary medicines to include 'non-efficacy' is very much welcomed; such a step should also be taken for human medicines.
- Attention should also be paid to the marketing activities by the pharmaceutical industry. The Commission should encourage the framing of ethical rules on the marketing of medicinal products including antibiotics at EU level, in conjunction with the pharmaceutical industry and all other relevant players. In this connection, methods should also be worked out for assessing and monitoring compliance with these ethical rules. When discussing this question account could inter alia be taken of the WHO's "Ethical Criteria for Medicinal Drug Promotion" and the IFPMA's "Code of Marketing and Promotion Practices" and of the way in which such criteria are adhered to.
- The Commission should encourage a survey in the Member States to ascertain whether trainee and qualified physicians, veterinarians and pharmacists receive sufficient instruction and continuing professional education in infectious diseases, infection control, antibiotics, antibiotic prescription and treatment, and antibiotic

resistance. Education and training of the medical profession is of key importance to control the emergence and spread of antibiotic resistance, as any action in this field will have an immediate effect.

- The Commission should initiate and promote a multi-media campaign by the Member States to inform the general public about infections, hygiene and antibiotics, so as to boost awareness of antibiotics and acquaint the public (e.g. parents, teachers, and school children) with the facts.
- The Member States should lend active support to the activities of the WHO Division of Emerging Diseases Surveillance and Control and its Antimicrobial Resistance Monitoring programme.

Brussels, 7 July 1998.