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VOLUME I

COMMUNICATION FROM THE COMMISSION

ON A COMMUNITY STRATEGY AGAINST ANTIMICROBIAL RESISTANCE

EXECUTIVE SUMMARY

The emergence and spread of antimicrobial resistance has become a major public health problem, within the Community and world-wide. Overuse and misuse of substances to kill or inhibit the growth of micro-organisms (including bacteria, viruses and fungae), and certain parasites (for example protozoa) have favoured the growth of resistant organisms. This so-called "antimicrobial resistance" can spread to other microbial populations. Infections by resistant organisms endanger the human population, animals and plants, including those not previously in contact with antimicrobial agents.

For the purposes of this Communication, the term "antimicrobial agent" encompasses a substance produced either synthetically or naturally by bacteria, fungae or plants, used to kill or inhibit the growth of micro-organisms, including bacteria, viruses and fungae, and parasites exhibiting the phenomenon of resistance (in particular protozoa). Antibiotics are substances with antibacterial effects.

Recent scientific opinions pointed out that prompt action is needed in the following areas: prudent use of antimicrobial agents, prevention of diseases, development of new products and methods of treatment and monitoring the situation.

Antimicrobial resistance is already addressed by the Community through various individual measures. The need is clear for an overall approach to this question, based on the provisions of Article 152 of the Treaty establishing the European Community which provides that a high level of health protection shall be ensured in the definition and implementation of all Community policies and activities.

On this basis, the Commission proposes to put in place a Community strategy on four key areas of action:

(1) **Surveillance**: Monitoring the evolution and the effects of interventions through the establishment/strengthening of accurate surveillance systems on antimicrobial resistance in the human and veterinary sector and the consumption of antimicrobial agents.

(2) **Prevention** of communicable diseases, and infection control to reduce the needs for antimicrobial agents. This includes the prudent use of antimicrobial agents which entails the need for improved product information for authorised antibacterial medicinal products and the promotion of educational and behavioural actions towards the professionals and the general public.

(3) **Research and product development**: New modalities for prevention and treatment of infections and continued support of research for new drugs and alternatives.

(4) **International co-operation**: Antimicrobial resistance does not respect frontiers. An effective strategy requires close co-operation and consultation between the Commission, the Member States and other involved parties, especially at international level.

The attached proposal for a Council Recommendation on the prudent use of antimicrobial agents plays an important part in the Community's multi-disciplinary and multi-faceted approach.

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(Text with EEA relevance)

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INTRODUCTION

Background

The discovery, development and availability of substances which kill or inhibit the growth of micro-organisms (bacteria, viruses and fungae), and parasites (for example protozoa) have over the last century revolutionised the treatment of infectious diseases, leading to a dramatic reduction in morbidity and mortality. Such "antimicrobial agents" (which for the purposes of this Communication include substances produced either synthetically or naturally by bacteria, fungae or plants, used to kill or inhibit the growth of micro-organisms, including bacteria, viruses and fungae, and parasites exhibiting the phenomenon of resistance, in particular protozoa, have greatly contributed to improvements in the health of the population. Antibiotics are substances with antibacterial effects.

However, disease-causing organisms have a remarkable ability to adapt themselves, notably to acquire and transmit antimicrobial resistance. Moreover, the excessive and uncontrolled use of antimicrobial agents favours the growth of resistant organisms and thus jeopardises the conquests of previous decades. Even though antimicrobial resistance from natural sources existed even before antimicrobial agents were introduced into medical treatment, it is generally accepted that there is an association between the quantities used and the increase in resistant organisms.

Despite ongoing research to find new groups of drugs to combat resistant organisms, it is uncertain if and when such drugs will be available. Therefore, antimicrobial agents must be used prudently in order to limit the further emergence and spread of resistant germs. Product development and product information must hold an important place within the strategy and the success of the actions to address antimicrobial resistance will need full support and contributions from the pharmaceutical industry as well as actions from governments.

At Community level, the problem of antimicrobial resistance has been recognised and addressed for several years. This document gives a **global overview** of the situation and sets out a Community strategy against antimicrobial resistance, including enhanced actions to address the problem which at international, Community and national level is seen as a growing and serious threat to health. In this context the various Recommendations of the Council, the Copenhagen Recommendations on antimicrobial resistance[1] endorsed by Council as well as the work of international organisations, in particular WHO and OIE, are significant.

The fight against emergence and spread of antimicrobial resistance is thus a **public health priority**.

Article 152 of the Treaty establishing the European Community provides the legal basis for action in the public health field. It stipulates that a **high level of health protection** shall be ensured in the definition and implementation of all Community policies and activities. The obligation thus lies with all Community institutions and with Member States.

The issue of antimicrobial resistance forms an inherent part of the Community's health strategy and comprises actions in all the relevant sectors: public health, veterinary and phytosanitary sectors. Under the Community Network for the Epidemiological Surveillance

[1] Report from the Invitational European Union Conference on "The Microbial Threat" hosted by the Danish Government in Copenhagen, Denmark, 9-10 September 1998.

of Communicable Diseases, surveillance of antimicrobial resistance is one of the priorities. Many initiatives and measures have been taken within the veterinary and phytosanitary sectors. As regards human medicine, a Commission proposal for a Council Recommendation on the prudent use of antimicrobial agents is attached to this communication. This represents another step in the Community's multi-disciplinary and multi-faceted approach to tackling antimicrobial resistance.

A Science Based Approach

The Community strategy on antimicrobial resistance is multidisciplinary and based on scientific advice.

On 28 May 1999, the Scientific Steering Committee (SSC) of the European Commission delivered an opinion on antimicrobial resistance[2]. The SSC's evaluation stated that prompt action was needed to reduce the overall use of antimicrobial agents in a balanced way in all areas: human medicine, veterinary medicine, animal production and plant protection. The strategies most likely to be effective in the control and containment of antimicrobial resistance will be those that can be introduced speedily without undue costs in all Member States, and which can be monitored and enforced across the EU. The SSC pointed to the possible need to introduce effective legislation and regulation to support the achievement of its proposals. The important areas of action identified concern the prudent use of antimicrobial agents, prevention, the development of new methods for prevention and treatment, and monitoring the effects of interventions.

A Comprehensive Action Plan to Combat Antimicrobial Resistance

The Commission has on this basis identified **four key areas of action** which form the major elements of the Community strategy to contain antimicrobial resistance:

(1) **Surveillance**: Monitoring the evolution and the effects of interventions through the establishment/strengthening of accurate surveillance systems on antimicrobial resistance in the human and veterinary sector and the consumption of antimicrobial agents.

(2) **Prevention** of communicable diseases, and infection control to reduce the needs for antimicrobial agents. This includes the prudent use of antimicrobial agents which entails the need for improved product information for authorised antibacterial medicinal products and the promotion of educational and behavioural actions towards the professionals and the general public.

(3) **Research and product development**: New modalities for prevention and treatment of infections and continued support of research for new drugs and alternatives.

(4) **International co-operation**: Antimicrobial resistance does not respect frontiers. An effective strategy requires close co-operation and consultation between the Commission, the Member States and other involved parties, especially at international level.

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[2] http://europa.eu.int/comm/food/fs/sc/ssc/out50_en.html

1. SURVEILLANCE, MONITORING AND DATA COLLECTION

1.1. Surveillance Networks on antimicrobial resistance

1.1.1. Human medicine

In January 1999, a Community Network for the Epidemiological Surveillance and Control of Communicable Diseases[3] was set up. Antimicrobial resistance is one of its priorities. The two main pillars of the Community Network for the Epidemiological Surveillance and Control of the Communicable Diseases are an early warning and response system on public health threats, and an epidemiological surveillance system on communicable diseases.

Surveillance of communicable diseases, especially monitoring of outbreaks and the timely exchange of relevant information on trends, is essential for intervention strategies on prevention and infection control. Quick co-ordinated action by the public health authorities of Member States is essential for the containment of morbidity and mortality which could emerge from rapidly spreading infections that do not respect borders. This can have an important impact on the reduction of antimicrobial treatment.

The progressive development of this Community network over the next five years will be an important step towards co-ordinated efforts among Member States, EEA/EFTA members and candidate countries regarding prevention of infections and containing resistant organisms.

Specific networks within the Community network framework are:

- **EARSS – European Antimicrobial Resistance Surveillance System[4]**

Comparison of resistance in the different Member States is biased by differences in the antimicrobial agents tested, the samples chosen for testing, the susceptibility test systems used and breakpoints adopted. To obtain more comparable and reliable data, the Commission has supported the Antimicrobial European Resistance Surveillance System (EARSS), an international network of national surveillance systems which, since 1998, aims to aggregate comparable and reliable antimicrobial resistance data for public health purposes in Europe The network is growing. At present 23 countries have agreed to participate in EARSS: the 15 EU Member States, Iceland, Norway, Hungary, Czech Republic, Bulgaria, Slovenia, Malta, Israel. In addition, Estonia, Poland, Slovakia, Romania, and Russia have expressed an interest in participation. Of the participating countries 18 have delivered data thus far. The estimated average coverage of the population of participating countries is 53% and ranges from 14% to 90%.

As far as future perspectives are concerned, the collection of routinely generated data could speed up the process of bringing more pathogens under surveillance. Progress has been made on software-tools to process and analyse resistance data. The next step will be to make this data widely accessible through the Health Surveillance System for Communicable Diseases within the European Public Health Information Network.

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3 Decision 98/2119/EC, OJ L 268, 3 October 1998

4 http://www.earss.rivm.nl

- **Enter-Net – International Surveillance Network for the Enteric Infections Salmonella and VTEC 0157**[5]

Enter-net was established in 1994 for the surveillance of salmonella and verotoxin-producing Escherichia coli (VTEC) infections. Since 2000, it has been an essential part of the Community network for epidemiological surveillance and control of communicable diseases. A major objective is rapid recognition of outbreaks of disease. Enter-net has contributed directly to the recognition of several international outbreaks and has enabled the subsequent investigations to be accelerated due to the efficient communication and collaboration within the network. It is also concerned with the surveillance of antibiotic resistance in enteric pathogens.

- **Euro-TB**[6]

The general objective of the Euro-TB programme for the Surveillance of Tuberculosis in Europe is to provide epidemiological information on tuberculosis (TB) to be used to improve TB control. Drug resistance is a key component of tuberculosis surveillance. Prevalence, particularly of multi-drug resistance (MDR), is important for public health as MDR-TB represents a major epidemic risk, particularly to immuno-suppressed individuals such as HIV-infected persons and those in institutions such as hospitals and care centers. Monitoring drug resistance is an important means to facilitate targeted control measures to reduce occurrence. The Euro-TB programme co-ordinated the elaboration of recommendations on the standardisation of antituberculosis drug resistance surveillance in Europe.

- **Nosocomial infections**

Nosocomial infections are infections occurring in a patient in a hospital which were neither present nor incubating prior to admittance but were acquired during hospitalisation. They also may occur in hospital personnel.

In 2000, a pilot project was started to develop a European Network on nosocomial infections. The main goals include the creation of databases on surgical and intensive care unit infections, the development of consensus for prevalence surveys, on validation of methods for the setting-up of evidence-based standards and recommendations and creation of the conditions for extended consensus surveys, training and fellowships.

1.1.2. Veterinary medicine

- **Monitoring and control of zoonoses**[7]

Community legislation on measures against zoonoses[8], at present under review, seeks to establish a reliable reporting system on the incidence of zoonoses in animals and humans. Currently the specific control measures provided by this Directive cover only the occurrence of two invasive *Salmonella* serotypes in poultry breeding flocks, frequently the origin of human salmonellosis from consumption of eggs. Two Community Reference Laboratories have been established to co-ordinate and harmonise the work of national laboratories and to

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5 http://www2.phls.co.uk

6 http://www.ceses.org/eurotb.htm

7 Any disease and/or infection, which is naturally transmissible directly or indirectly from animals to humans

8 Council Directive 92/117/EEC, OJ L 62, 15 March 1993

collect data on zoonoses including some information of antimicrobial resistance in zoonotic bacteria.

Member States have submitted yearly reports since 1995 on the occurrence of certain zoonotic organisms. However, the collection of resistance data linked to this reporting is not yet harmonised, and the methods used for testing resistance differ between Member States.

In addition to these horizontal provisions, requirements on the control of certain zoonoses (e.g. tuberculosis, brucellosis) at farm level have been laid down in various directives regarding animal health conditions. Specific measures on the control of zoonotic agents in processing and distribution of foodstuffs of animal origin are contained in the corresponding hygiene directives.

The Commission has clearly identified food safety as one of its top priorities. The White Paper on Food Safety[9] sets out the plans for a proactive new food policy following the "farm to fork" principle by in particular modernising legislation to form a coherent and transparent set of rules in order to produce safer food from healthier animals. This policy needs to take account of the prevalence of zoonotic agents in the Member States and to give guarantees for the improvement of the safety of consumers by introducing pathogen reduction programmes to be implemented by the Member States.

In the framework of the review of the zoonoses legislation, the Commission is considering the possibility to introduce a requirement to monitor antimicrobial resistance in certain zoonotic micro-organisms, like salmonella and campylobacter, in certain animal populations. A proposal for new legislation to improve monitoring and reporting of systems for diseases transmissible from animals to man is foreseen to be submitted in 2001.

- **Monitoring antimicrobial resistance**

In addition to initiatives concerning zoonotic agents, monitoring antibiotic resistance in bacteria of animal origin is a concerted action[10] in the Community. This action aims to harmonise the antibiotic resistance monitoring in Europe and to develop research projects aiming at better understanding the mechanisms of emergence and spread of resistance within a species, and from animal to man and environment.

The Commission introduced the requirement to monitor resistance in animal bacteria of feed additive antibiotics and substances related to them in Commission Directive[11] suspending the use of avoparcin as a feedingstuff additive in January 1997. This obligation was reconfirmed in the Council Regulation[12] of December 1998 suspending the use of four other antibiotics used as growth promoters in feedingstuffs as a condition to re-examine the issue.

The Commission has also supported an industry-led surveillance programme on resistance to antibiotics used as feed additives in bacteria isolated from pigs and broilers in the slaughterhouses in six European countries. A report will be provided in the near future.

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9 http://europa.eu.int/comm/dgs/health_consumer/library/pub/pub06_en.pdf

10 FAIR5-CT97-3654

11 Directive 97/6/EC, OJ L 35, 5 February 1997

12 Regulation 2821/98, OJ L 351, 29 December 1998

However, it should be ensured that surveillance systems are established which provide the collation of resistance data from all relevant bacteria in animals and foodstuffs at the Community level.

1.2. Monitoring of antimicrobial consumption

1.2.1. Humans

Sound data on the consumption of antimicrobial agents is needed for the development of intervention strategies. Such data already exist in many Member States but they are scattered, heterogeneous, and in many instance not easily accessible. This data needs to be accessed, collected and analysed to enable the development of a Community-wide surveillance system on the use of antimicrobial agents and procedures for intervention measures. The attached Commission proposal for a Council Recommendation on the prudent use of antimicrobial agents in human medicine addresses this problem.

1.2.2. Animals

- **Veterinary medicines**

Only a few Member States currently monitor the consumption of antimicrobial agents as veterinary medicinal products. This kind of consumption data is nevertheless essential for the assessment of the risk from the transfer to humans of resistant micro-organisms in animals. Further action at Community level should be considered on this aspect.

- **Feed additives**

Following the Copenhagen Recommendations, a system has been established to collect data on the supply and consumption of antimicrobial agents as additives in feeding stuffs, both as veterinary medicinal products and growth promoters. On the basis of guidelines for the collection of the relevant information agreed in the Standing Committee for Animal Nutrition, the monitoring started in January 2000. The first results should be available by mid 2001.

1.2.3. Plant Protection

The use of antibiotics in plant protection is monitored in all Member States, where such uses are available. Total prohibition of antibiotics are effective in Sweden, Finland, Italy, Portugal, Ireland, Luxembourg, Denmark, France, United Kingdom and Germany. The Standing Committee for Plant Health already in 1999 has established a procedure to collect data from those member States which still allow the use in emergency situations and keeps the survey available.

1.3. Safety evaluation of antimicrobial agents used in plant protection

Community legislation on plant protection products[13] provides the legal basis also for the evaluation of antibiotics used in plant protection. All data requirements and decision-making criteria laid down in the Directive apply in principle also for antibiotics used. However, in view of the prohibition of such uses in a majority of the Member States and the minor amounts used and restrictions imposed in others, the Commission has set other priorities for the ongoing review programme under the Directive. Antibiotics currently in use in the

[13] Directive 91/414/EEC, OJ L 230, 19 August 1991

Community will be reviewed under the third stage of the review programme, which will begin in 2002.

Fungicides are authorised in all Member States and the active substances are being reviewed in the ongoing programmes under Directive 91/414/EEC.

2. TOWARDS AN IMPROVED SYSTEM OF PREVENTION AND CONTROL

2.1. Market authorisation and user information on antimicrobial agents

2.1.1. Human medicine

The European Agency for the Evaluation of Medicinal Products (EMEA) is involved in activities which focus on requirement for market authorisation and on the quality and content of the Summary of Product Characteristics (SPC) which, in particular, lays the basis for all promotional activities of an antimicrobial agent.

The EMEA has published a discussion paper on antimicrobial resistance[14] outlining its activities and pointing out the need to find ways to promote new effective antibiotics so as not to prematurely exhaust their potential clinical benefits.

Criteria for market authorisation of new antibacterial medicinal products are outlined in three EU guideline documents that became operational in 1997 and 2000 (14-16)[15]. In particular, information on acquired resistance for relevant bacteria/antibiotic combinations has to be regularly updated by the marketing authorisation holders. A better rational for giving dose recommendations for antibiotics has also been addressed in one guideline. It may be assumed that better dose recommendations will contribute to optimal treatment of infections and a reduction in unnecessary and inappropriate use of antibiotics.

Concerns have been expressed by regulators in different European authorities that different indications, doses, dose regimens (duration of treatment) and different pharmacodynamic information exist for the same and similar products already licensed in the EU. National competent authorities in consultation with EMEA are currently considering the issue of divergent product information.

2.1.2. Veterinary medicine

The authorisation of veterinary medicinal products should ensure that recommended dosages and treatment regimes are optimum to minimise the development of resistance. Moreover, susceptibility patterns of populations of target bacteria may need to be monitored after the authorisation.

The Committee for Veterinary Medicinal Products (CVMP) of the EMEA pointed out in its Report on Antimicrobial Resistance and Qualitative Risk Assessment that the vast majority of antibiotics used in veterinary medicine are related to, or identical to, human medicinal products and can select for cross-resistance or co-resistance. It also identified a lack of data and of harmonisation which prevent a coherent and scientific approach at European level. Furthermore, a Risk Management Strategic Plan has been developed setting out proposals on

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14 EMEA document 9880/99: http://www.eudra.org/humandocs/humans/general.htm

15 EMEA documents CPMP/EWP/558/95, CPMP/EWP/520/96, CPMP/EWP/2655/99

the containment of antimicrobial resistance and the following major areas of CVMP activity are currently underway:

a) Critical evaluation of the data related to minimum inhibitory concentrations (MICs) and of the current relevance of using MIC and kinetic data in the setting of dosage levels.

b) Development of guidelines to satisfy the requirements for the resistance section in a regulatory dossier for antimicrobial agents, with particular emphasis on a description of the testing aimed at establishing the likelihood of resistance development to novel antimicrobial agents, i.e pre-authorisation sensitivity testing guidelines.

c) Consolidation and standardisation of phrases and formats used in the Summary of Product Characteristics to define clearly and consistently throughout the European Union posology/treatment regimes, target organisms and diseases in accordance with prudent use principles.

d) Development of definitive guidelines for antimicrobial prophylaxis, combination therapies, in-feed and water mass medication, given that resistance is driven by the volume of active use and the route of administration.

2.2. Prudent use of antimicrobial agents

2.2.1. Human medicine: Commission proposal for a Council Recommendation

The Commission has developed a proposal for a Council Recommendation on the prudent use of antimicrobial agents in humans, attached to this communication.

The main elements of this proposal are the following:

- **Collection and analysis of data** on antimicrobial resistant pathogens and on consumption of antimicrobial agents to identify potential links for intervention measures;

- Enforcing the principle that antibacterial substances should be available by **prescription only**, and evaluating whether this rule should be applied to all antimicrobial agents as a precaution;

- Developing guidelines and principles on the **prudent use** of antimicrobial agents, including systems for evaluation;

- Improving **prevention** of infections to reduce the needs for antimicrobial agents by reinforcing immunisation programmes and developing infection control standards in hospitals and the community;

- Raising awareness of the problem of antimicrobial resistance by **information to the general public**;

- Enhancing knowledge on the problem by **education programmes for health professionals**;

- Encouraging **research** on the development of antimicrobial resistance and the development of rapid diagnostics to enable efficient early treatment of communicable diseases;

- Nominating, for these purposes, a multi-disciplinary and cross-sectoral national organisation to ensure mutual information and **co-ordination** of efforts.

2.2.2. Veterinary medicine

An important element in ensuring the prudent use of antimicrobial agents in veterinary medicine is the monitoring of residues in food. Community legislation[16] requires monitoring of certain substances (including antimicrobial agents) or residues in live animals and animal products. Levels of sampling are governed by Council Directive 96/23/EC, and maximum residue limits are fixed according to scientific advice, under Regulation (EEC) 2377/90. Member States and Third Countries (for the products they export to the EU) provide the Commission with yearly results of the monitoring according to their residue plans which have to be approved by the Commission. Compliance with EC requirements is moreover regularly checked on site by the Commission Food and Veterinary Office.

Currently, samples with positive findings on residues represent less than 1% of the total. However, within these positives, antibiotics represent approximately 70%. Although current legislation, through Directives 81/851/EEC and 81/852/EEC, establishes harmonised requirements for marketing authorisations in the European Union, and Regulation (EEC) 2377/90 ensures a harmonised procedure for the authorisation of analytical methods, the significant number of substances on the market authorised over the years, identifies the need that national competent authorities in connection with the EMEA further consider the issue of divergent product information.

There have been several public and private actions taken in the Member States and at the international and European level to produce guidelines on the prudent use of antimicrobial agents as veterinary medicines. For example the Federation of Veterinarians of Europe (FVE) has prepared a guide on prudent use of antibiotics in veterinary medicine and in addition to that some Member States have their own national guidelines. Also the World Organisation for Animal Health (OIE) and the Codex Alimentarius are currently working with issues related to prudent use of antimicrobial agents in animals, the OIE having just published principles on prudent use. In order to harmonise these actions at the Community level it should be considered whether comparable measures to those proposed in the Recommendation on the prudent use in humans are necessary in the veterinary field. In particular, emphasis should be given to the prevention of infectious diseases in animals, as it is an effective way to decrease the quantities of antimicrobial agents used. In addition it is vital to encourage the Member States to strengthen their controls on illegal distribution and use of antimicrobial agents in agriculture thus diminishing the possibilities for imprudent use of the substances.

2.3. Additives

2.3.1. In food

The use of food additives is harmonised in the European Union. Community legislation on food additives[17] lays down the principles for approving food additives and their uses in foodstuffs. Two antimicrobial agents, Nisin (E 234) and Natamycin (E 235), are authorised for preservation of certain foods. The Commission will review the safety and need for the use of these substances.

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16 Council Directive 96/23/EC, OJ L 125, 23 April 1996.

17 Council Directive 89/107/EEC, OJ L 40, 11 February 1989

2.3.2. Phasing out and replacement of antimicrobial agents as growth promoters in animal feed

The Commission has paid increasing attention to the need to restrict antibiotic use to serious human and animal health problems. Indeed the number of antibiotics authorised as growth promoters in animal nutrition has been constantly decreasing. Following the bans on avoparcin in January 1997, ardacin in January 1998, and in December 1998 of a further four antibiotics (bacitracin zinc, virginiamycin, tylosin phosphate and spiramycin), there are only four substances still authorised as growth-promoting agents. These substances do not belong to classes used in human and/or veterinary medicine. Following a review of further evidence, the Scientific Steering Committee has recently concluded that the evidence justifying the original ban of these substances remains valid.

However, as set out in the White Paper on Food Safety, the Commission will pursue the prohibition or phasing-out of antibiotics used as growth promoters in the EU as part of its broad strategy to control and contain antibiotic resistance.

In the meantime, it is necessary to carry out studies on the most critical sectors (in particular for piglets and broiler production) to minimise possible economic losses or the increase in use of antibiotics for treatment under veterinary prescription. The studies should estimate the gap between the current situation and the husbandry standards which will be required following the abolition of antimicrobial growth promoters.

The Commission supports the view that the phasing out would also be easier to pursue if other classes of growth promoting additives were made available. In this respect nineteen micro-organisms have been authorised so far and others are very near to being authorised. An application to authorise an organic acid as a growth promoter is under examination and Member States have received several other requests for authorisations for other types of products which have a positive effect on animal production.

A proposal to phase out the four remaining antimicrobial feedingstuff additives by January 2006 is in preparation and is expected to be adopted by the Commission in the near future.

2.4. Antimicrobial resistance as markers of Genetically Modified Organisms (GMOs)

The SSC has recommended to remove antibiotic resistance marker genes from plant cells before commercialisation whenever this is feasible. Whilst this is possible in the case of more recent constructs, it would prove difficult or impossible for older products. In the latter case, the clinical importance of the respective antibiotic and gene promoter, a regulatory DNA sequence that functions to activate expression of genes, has to be taken into account before authorisation.

Community legislation on the deliberate release of genetically modified organisms has been revised recently and the new Directive 2001/18/EC came into force on 17 April 2001[18]. Member States shall implement this Directive into national legislation by 17 October 2002. Directive 2001/18/EC provides that Member States and the Commission shall ensure that GMOs which contain genes expressing resistance to antibiotics in use for medical or veterinary treatment are taken into particular consideration when carrying out an environmental risk assessment, with a view to identifying and phasing out antibiotic

[18] OJ L 106, 17 April 2001

resistance markers in GMOs which may have adverse effects on human health and the environment.

3. PREPARING FOR THE FUTURE

Research targeted at antimicrobial resistance has long played a part in Community research. In the Fourth Framework Programme for Research and Technological Development (1994-1998)[19] and in the current Fifth Framework Programme (1998-2002)[20], several projects contribute directly or indirectly to the different pillars of a medium to long-term approach to antimicrobial resistance. Most of the relevant research topics are covered by the key action 2 "Control of Infectious Diseases" of the Quality of Life Programme, where ongoing research projects address the following issues:

- **Vaccines** against tuberculosis, malaria, HIV and other major diseases ultimately to contribute to reduced morbidity and thereby the need for antimicrobial treatment.

- Development of **new classes of antimicrobial agents** against multi-drug resistant strains of serious pathogens (e.g. *Mycobacterium tuberculosis*) and other new treatment strategies, such as conjugation inhibitors or efflux pump inhibitors.

- Development of **rapid and reliable diagnostic and susceptibility tests** as an essential prerequisite for the prudent prescription of antibiotics.

- Identification of **new strategies to reduce the spread of infections** in day-care centres.

- Improved understanding of the molecular mechanisms behind the development, spread and reversibility of antibiotic drug resistance.

- Evaluation and harmonisation of strategies for prevention and control of antibiotic resistant pathogens in European hospitals.

Other key actions in the Quality of Life Programme address issues which complement the above outlined priorities. Key action 1 'Food, Nutrition and Health' focuses on transfer mechanisms of antibiotic resistance between animal, microbial and human reservoirs via food ingestion; development and validation of rapid and/or cost-effective detection tests of antibiotics; as well as pro- and pre-biotics combinations as alternatives to today's antibiotics. Key action 3 'The Cell Factory' focuses on design and development of new **antimicrobial agents** as well as near-patient diagnostic tests and key action 4 'Environment and Health' on environmental factors influencing transmission. Key action 5 'Sustainable agriculture, fisheries and forestry, and integrated development of rural areas including mountain areas' aims at new strategies for reducing antibiotic use in animal husbandry.

The Commission's Joint Research Center is involved in the development of analytical methods and reference materials to be used for detection of antibiotic residues in various foods and feeds.

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[19] OJ L 126, 18 May 1994

[20] OJ L 26, 1 February 1999

The Commission has presented its proposal for the next framework programme (2002-2006)[21], hightlighting the fight against resistance to drugs as a priority.

4. INTERNATIONAL CO-OPERATION

Tremendous expansion in global trade and travel has increased the speed of spread of disease and of antimicrobial resistance between countries and continents. Antimicrobial resistance does not respect borders and concerns the entire world; it cannot be tackled successfully by a single country or even by a group of countries. Concerted international action is therefore a key element in the approach to this problem.

Intensive co-operation is already in place with many non-EU countries. In the context of the future enlargement of the Union, a special emphasis has been placed on co-operation with the candidate countries, who already take part in several health programmes and are included in most of the European surveillance networks.

Developing countries cannot be left aside, and assistance is provided to them throughout all the fields of the fight against antimicrobial resistance: surveillance networks, data gathering, research and licensing procedures of new drugs and vaccines, disease prevention, education of prescribers. Of note is the EC Development Policy[22]. Support is also provided to fight against counterfeit drugs which, in addition to the economic losses they cause to the pharmaceutical sector, have a great influence on the spread of antimicrobial resistance (inappropriate dosage and duration of treatment, reduced efficiency).

This international co-operation requires the involvement of national governments and agencies, non-governmental organisations, professional societies and international agencies. It needs to generate a synergy and avoid conflicting messages. Data and information on experience should be shared between all parties to maximise the success of all strategies. There is also great progress to be made in the harmonisation of data gathering, in order to be able to exploit them at the international level.

In that context, the Commission has put in place several important links:

– The **World Health Organisation** (WHO) and the European Commission recently reconfirmed their common interests in health and health related fields with the signing of a Memorandum of Understanding. Linking communicable disease and health monitoring networks and the development of methodologies and standards for addressing antimicrobial resistance threats are agreed priorities for future co-operation. The WHO has participated in developing the attached proposal for a Council Recommendation on the prudent use of **antimicrobial agents** in humans. The Commission contributes to WHO activities on establishing a global strategy for the containment of antimicrobial resistance.

– The **Codex Alimentarius** is also concerned by antimicrobial resistance, in particular as regards maximum residue limits in food. Steps are being taken for the European Community to become a member as such of the Codex Alimentarius together with the Member States and will promote and encourage a concerted and harmonised approach.

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21 OJ …

22 COM(2000) 585 final and COM(2001) 96 final

– The ***Office International des Epizooties*** (OIE - the international organisation for animal health) has clearly established antimicrobial resistance as one of its priorities for coming years and has conducted a world-wide consultation on its recommendations relating to control of antibiotic resistance.

– An **EU/US Task Force on communicable diseases** was created in 1995 as part of the Joint EU-US Action Plan to implement the New Transatlantic Agenda. Work related to combating antimicrobial resistance is a EU/US Task Force priority, with a specific working group on the subject.

– In June 2000 the Heads of Governments and States of the Member States of the European Union adopted the **Northern Dimension Action Plan** and invited the European Commission to take a leading role in its implementation. Within its objectives on public health, the surveillance and control of communicable diseases are described as priorities, including actions on antimicrobial resistance.

– The **Baltic Sea States Task Force on Communicable Diseases Control** in its last meeting at the end of 2000 in Copenhagen issued recommendations on antibiotic resistance: prescription only drugs, collection and exchange of data, improvement of diagnostic, surveillance networks and early warning systems, training of staff.

– The first **Euro-Med** Conference of Health Ministers in Montpellier on 3 December 1999 agreed that the European Community Network for the Epidemiological Surveillance and Control of Communicable Diseases is an important element in strengthening co-operation in public health.

CONCLUSION

The following list details the priority actions in the **four identified key areas** of the Community strategy against antimicrobial resistance, which complement the specific Recommendation on the prudent use of antimicrobial agents.

Surveillance

Action 1:Develop co-ordinated and coherent surveillance networks at the European level. Encourage the participation of non-EU countries and the links between already established surveillance networks in human and veterinary medicines

Action 2:Put in place and improve the collection of data on consumption of **antimicrobial agents** in all sectors.

Prevention

Action 3:Increase the importance of antimicrobial resistance information for the market authorisation process in human medicine, veterinary medicine and agriculture.

Action 4:Support, at Community level, educational campaigns directed at professionals (clinicians, veterinarians, farmers) and the general public to avoid overuse and misuse of antimicrobial agents.

Action 5:Fully apply the principle that antibacterial substances are available in human and veterinary medicine by prescription only and distributed in a controlled way in agriculture, and evaluate whether the prescription-only rule should be applied to all **antimicrobial agents** as a precaution.

Action 6:Reinforce and promote prevention programmes of infections in human and veterinary medicine, in particular immunisation programmes.

Action 7:Reinforce the residue monitoring system in food as regards methods of analysis, sanctions and reporting system.

Action 8:Phase out and replace **antimicrobial agents** used as growth promoters in feed.

Action 9:Review the use of the two authorised antimicrobial agents in food.

Action 10: ensure that GMOs which contain genes expressing resistance to antibiotics in use for medical or veterinary treatment are taken into particular consideration when carrying out an environmental risk assessment, with a view to identifying and phasing out antibiotic resistance markers in GMOs which may have adverse effects on human health and the environment.

Research and product development

Action 11:Encourage the development of new **antimicrobial agents**.

Action 12:Encourage the development of alternative treatments and vaccines.

Action 13:Support the development of rapid and reliable diagnostic and susceptibility tests.

International co-operation

Action 14:Encourage strongly the development of co-operation, co-ordination and partnership at international level in particular via the existing international organisations.

Action 15:Pay special attention to candidate and developing countries by helping them putting in place the appropriate structures.