The European Agency for the Evaluation of Medicinal Products

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EMEA Discussion Paper on Antimicrobial Resistance

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EMEA DISCUSSION PAPER ON ANTIMICROBIAL RESISTANCE

Problem statement

There is concern that some antibiotics are rapidly losing their effectiveness as resistance is spread within and between different bacteria.

In man this problem is caused largely by uncontrolled and inappropriate use of antibiotics but other factors such as crowding of patients in hospitals, food-globalisation and increased travelling of people between different geographic areas contribute to the spread of bacterial resistance. More restricted use advantageously reverts resistance, although this may not always be expected. The EMEA through its Committee for Proprietary Medicinal Products cognisant of the public health concerns has addressed the problem by giving guidance to industry and regulatory assessors on the necessary information in the product information and further in the European Public Assessment Report.

Whilst the concerns being highlighted both globally and within the Community relate primarily to the growing incidence of resistance to antimicrobials in man; the potential contribution to this phenomenon by the use of these products in animals both for therapeutic and growth promotion use is gaining widespread attention. The EMEA through its Committee for Veterinary Medicinal Products in 1997 agreed that the subject of antimicrobial resistance in animals resulting from therapeutic use of antibiotics in the veterinary sector and its potential transfer to man merited a detailed investigation with a view to producing a CVMP position paper with appropriate recommendations, based on a Risk Assessment approach. Its Report is expected to be released to the public in the second quarter of this year.

Overview of initiatives in the European Union

The resistance problem issue has attracted much concern and different initiatives have been taken or are envisaged to cope with the situation in the EU. The following examples could be given involving the European Commission and its different Directorate Generals, the Member States, WHO and bodies like the Economic and Social Committee and Learned Societies:

- A multidisciplinary scientific approach integrating epidemiology, laboratory aspects, and interventions should be promoted.
- Co-ordinated research on antimicrobial resistance mechanisms should be made a high priority
- The implemention of a coordinated research program to document the impact of antimicrobial resistance on society, priority should be given to studies on human morbidity and mortality, including risk assessment and the estimation of the cost of infections due to resistant microorganisms
- Surveillance systems need to be put in place to gather reliable data on the prevalence of resistance over time in different geographic areas for antimicrobials used singly and relevant antibiotic/-bacterial combinations both in animals and in man in a coordinated and properly funded research program
- The judicious use of antibiotics among prescribers (physicians and veterinarians) and patients, both animal and human must be a primary educational concern.
- Conferences convened by WHO and Member States to address the significance of the potential contribution to the problem form use of antimicrobials in animals (therapeutic and growth promotion).

Role of the EMEA

The European Commission, EMEA and the competent authorities of the Member States hold responsibility for safe and efficacious medicinal products made available through the centralised procedure and the mutual recognition procedure. Via EMEA's scientific Committees for Medicinal Products for Human use (CPMP) and for Medicinal Products for Veterinary use (CVMP), quality, safety and efficacy of a new antibacterial medicinal product are to be safeguarded.

As EU regulatory body, the EMEA has to contribute to the protection and promotion of public and animal health. This has regulatory implications to support

- control of overuse-misuse of antibiotics
- design and implementation of measures aimed at controlling antibiotic resistance

The EMEA with its scientific body (CPMP) for human medicinal products has taken the following actions:

- A recently introduced CPMP Guideline (CPMP520/96) addressed to industry and to regulatory assessors provides guidance on how to prepare product information for health professionals and patients before introducing a new antibiotic. The problem arising from varying resistance in the different geographic areas of the EU has been recognised. Special consideration has been given to the Summary of Product Characteristics (SPC) information on the range of acquired resistance, which has to be included in the section on pharmacodynamic properties in the SPC. The importance of making available information on resistance locally becomes particularly obvious when severe infections are to be treated as is mentioned in this section of the SPC. The Marketing Authorisation Holder, therefore, needs to provide and update information on resistance to furnish clinicians with relevant information when prescribing these products for infections caused by targeted micro-organisms.

- The European Public Assessment Report (EPAR) includes the Summary of the Product Characteristics (SPC) as well as the Package Leaflet in the 11 relevant languages. In addition, in the section giving the scientific basis for the CPMP approval, substantiation of the statements made in the SPC are made. Information on the number and characteristics of patients making up the database on the prevalence of resistance in the European Union will be described along with the methods used for setting tentative breakpoints for relevant antibiotic/pathogen combinations where appropriate. Any follow-up studies which will be performed by the applicant and which is aimed at complimenting information on local resistance will also be mentioned in the EPAR.

- The CPMP has also agreed to cross-refer in a SPC for a centralised antibiotic to official guidelines.

- Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance. A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy. The possibility to produce such a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP working parties.

The EMEA with its scientific body (CVMP) for veterinary medicinal products has taken the following actions:

- The CVMP has created in June 1997 an ad-hoc group of scientific experts. The mandate of the group is to conduct an in-depth scientific assessment of the incidence of antimicrobial resistance within all Member States of the EU among bacteria isolated from animals. Consideration is being given to determining the degree at which resistance might affect the efficacy of antibiotics in animals today and in the future, the distinction between genetic and transferable resistance, and the impact all this may have on the success with which antibiotics are used in treating animals. Furthermore, the group is to assess the risk of transfer of resistance from animal bacteria to man and to what degree this phenomenon might occur.
  The working group is initially focussing on a qualitative risk assessment concentrating on the major zoonotic organism *Salmonella typhimurium* against one class of antimicrobials namely the fluoroquinolones. (Further consideration will have to be given to expanding the first report into a full quantitative risk assessment once the first report is released contingent on resources and funds being available). Once the first phase is completed the CVMP will consider ways of managing the problems of resistance in the veterinary sector with a view to reducing risk of transfer to man. Options may include selective use recommendations, restrictions of certain classes of antimicrobials for animal use and post marketing surveillance in accordance with accepted criteria within the precautionary principle.

- The CVMP has also included the need for extra focus on this issue in its Guidance note on Pharmacovigilance for veterinary Pharmaceuticals (EMEA/CVMP/183/96-FINAL) which came into effect on 1 January 1998, wherein companies are now required to report any evidence of inefficacy of its products. In the case of antimicrobials monitoring for such evidence of lack of efficacy through epidemio-surveillance will provide means of detecting early signs of resistance development. In a draft guideline for the conduct of post marketing surveillance studies of veterinary medicinal products, which is currently out for consultation (EMEA/CVP/044/99), consideration is being given to including the monitoring of resistance as part of such a surveillance scheme for antimicrobials.

Discussion

The EMEA and its scientific bodies, cognisant of the public health concerns posed by the emergence of antibiotic resistance have implemented measures and initiatives to further alert prescribing physicians and health care workers to the problem.
Further regulatory initiatives may become necessary following an agreed and comprehensive European action plan to combat this serious threat to public health.
In particular, it could be argued that the misuse of antibiotics is partly a consequence of the indications granted by regulatory authorities in the past, is being too broad to allow judicious promotion of antibiotics.
If the public health concerns on resistance development are such that stricter marketing authorisation criteria for antibiotics are warranted, the current criteria for marketing authorisation may need to be modified.
However, this issue needs to be carefully considered. EMEA with its scientific bodies, the National Competent Authorities, the European Commission, industry and learned societies will need to cooperate to clarify the consequences of such a proposal. The overriding concern here is to find ways of promoting new effective antibiotics so as not to prematurely exhaust their potential clinical benefits.

The EMEA invites comments on the situation and on the proposals described for its activities.

Any comment should be sent to Dr Bo Aronsson at the EMEA before end of July 1999.

