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Innovative Incentives for **Effective Antibacterials**

Executive Summary

The Swedish Government is concerned about the increasing frequency of multidrug-resistant bacteria that pose a major threat to human health and cause significant morbidity and mortality in Europe and the rest of the world. This is also associated with significant costs for society. Moreover, a number of advanced interventions that we take for granted, e.g. surgery, cancer treatment, transplantation and care of premature babies, may be impossible when effective antibacterials are no longer available. Resistance will naturally evolve as a cause of the use and misuse of antibiotics. For several decades, new classes of effective antibiotics were regularly developed, but over the last 40 years only two new classes of antibiotics have reached the market. This is largely a market failure as antibacterials provide less return than drugs for other indications. To overcome this problem, a variety of measures have to be taken, and the present conference is one step in that direction. The conference called on a unique mix of experts representing the European Commission, EU agencies, governments, academia, the European Federation of Pharmaceutical Industries and Associations, NGOs and other organisations, as well as regulators of pharmaceutical products. The conference was preceded by a workshop session addressing the possibilities of regulatory, financial and legislative options and research strategies to enhance the possibilities of getting new and much needed products to the patients. The results of the conference will form the basis for Council conclusions for the health ministers to adopt at the meeting of the Employment, Social Policy, Health and Consumer Affairs Council (EPSCO).

“Antibiotic resistance is one of the questions I have assigned highest priority to during our EU-Presidency. The conference on 17 September has given a clear signal that we are facing a very important challenge as regards access to effective antibiotics. Thanks to the unique expertise gathered in Stockholm, it is clear to us all that this problem is urgent and requires action at all levels. We are about to find ourselves in a situation with a growing number of severe infections against which no antibiotics are effective. However, the conference shows that there are a number of potential ways forward to be explored. I set great hopes on this event as the starting point for common and decisive action in this field.”

Göran Hägglund
Minister for Health and Social Affairs

Introduction

On 17 September 2009, the Swedish Presidency of the EU hosted an expert conference, *Innovative Incentives for Effective Antibacterials*, focusing on the increasing global threat of antibiotic resistance. The aim of the conference was to explore ways of creating incentives for the development of new medicines effective against multidrug-resistant (MDR) pathogens. The conference took place in Stockholm and was preceded by three workshops for invited experts, held on 16 September. On the day of the conference, two important reports were made publicly available: *Policies and incentives for promoting innovation in antibiotic research*, commissioned by the Swedish Government and written by Professor Elias Mossialos and his co-workers at the London School of Economics and Political Science on behalf of the European Observatory for Health Systems and Policies; and *The bacterial challenge: Time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents*, jointly written by two European agencies, the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMEA) in collaboration with the international network Action on Antibiotic Resistance, ReAct. In addition to these two reports, a recent report from the Swedish Governmental Agency for Innovation Systems (VINNOVA), with the aim of "surveying and analysing the prevailing conditions for innovations being developed that are intended to supplement the traditional use of antibiotic drugs", as well as the outcome of the three workshops formed a background for the discussions and outcome of the conference.

The conference was co-funded by the European Commission, and organised in cooperation with the Swedish Institute for Infectious Disease Control, the Swedish Strategic Programme against Antibiotic Resistance (STRAMA), the European Observatory on Health Systems and Policies, the European Centre for Disease Prevention and Control (ECDC), the Medical Products Agency, the National Board of Health and Welfare, Action on Antibiotic Resistance (ReAct) and the European Medicines Agency (EMEA).

1. Welcoming address

The Swedish Minister for Health and Social Affairs, Mr Göran Hägglund, opened the conference by stressing that the meeting had been designated a high priority of the Swedish Presidency. He pointed out the marked change over recent decades in the availability of efficient antibiotics to treat infections caused by resistant bacteria. Previous Presidencies – those of Slovenia, France and the Czech Republic – have given priority to different aspects of the problem of increasing antibiotic resistance by focusing on infection control and patient safety, the rational use of antibiotics and raising awareness among the public. There is a risk that society could return to the conditions of the pre-antibiotic era, which would make a number of advanced medical interventions impossible, e.g. hip replacements, transplants, saving premature infants and cancer treatments. Mr Hägglund expressed his satisfaction at having commissioned the investigation from the European Observatory, and noted that its publication had made the conference possible. Based on the current alarming situation regarding antibiotic resistance, the Swedish EU-Presidency is aiming for Council conclusions in this field to be adopted later this year by the EPSCO Council on 1 December 2009.

2. Antibacterial resistance – the problem and its consequences

Professor Otto Cars, the Director of Strama (the Swedish Strategic Programme against Antibiotic Resistance) and the international network Action of Antibiotic Resistance, ReAct, – a network that provides great inspiration in the quest for new antibiotics and in the struggle for the rational use of antibiotics – gave an overview of the global problem. At the beginning of the antibiotic era there was unprecedented success, e.g. a reduction of pneumonia mortality from 90 per cent to 10 per cent. Although the discoverer of penicillin, Sir Alexander Fleming, warned against resistance, the drug was indiscriminately promoted with slogans like "penicillin for every indication". Bacteria are our passengers and we live in happy coexistence with most of them. They also travel easily with us, something that was demonstrated by the fast worldwide dissemination of a resistant pneumococcus clone, first appearing in Spain. The increasing frequency of resistant strains means increased morbidity and mortality, increased health costs and increased suffering. According to recent WHO data, infectious diseases are still the second biggest killer in the world. The consequences of the increasing number of infections caused by MDR (multiple drug-resistant) bacteria, where the treatment options are very limited or non-existent, are a substantial rise in morbidity and mortality at a major cost for society. This situation is already a worrying reality in several EU countries. Everyone is responsible for the situation and everybody has to be part of the solution. Today it is clear that action on governmental and EU levels is needed, not only to handle the available agents in a responsible way so as to preserve their effectiveness, but also to promote the development of new antibacterial agents to fill the gap that has been identified between treatment needs and available therapeutic options.

3. The gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents

The 'GAP analysis', *The bacterial challenge: Time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents*, made public at this EU conference, was presented by two European agencies, ECDC and EMEA. The ECDC/EMEA joint working group was given the task on 28 February 2008 of overseeing, facilitating, following up and being a part of the work to produce a report on the gap between the increasing prevalence of multidrug-resistant bacteria and antibacterial drug development aimed at treating such infections.

Dr Dominique Monnet from the European Centre for Disease Prevention and Control (ECDC) reported on the trends and burden of infections due to multidrug-resistant bacteria in the EU.

Data on selected antibiotic-resistant bacteria in invasive infections (mainly bloodstream infections) of public health importance were available from the European Antimicrobial Resistance Surveillance System (EARSS) for EU Member States, Iceland and Norway for each year during the period 2002–2007. The following antibiotic-resistant bacteria were selected:

- *Staphylococcus aureus*, methicillin resistance (MRSA)
- *S. aureus*, vancomycin intermediate resistance and vancomycin resistance (VISA/VRSA)
- *Enterococcus spp. (e.g. Enterococcus faecium)*, vancomycin resistance (VRE)
- *Streptococcus pneumoniae*, penicillin resistance (PRSP)
- *Enterobacteriaceae (e.g. Escherichia coli, Klebsiella pneumoniae)*, third generation cephalosporin resistance (also referred to as ESBL-producing bacteria)

- *Enterobacteriaceae (e.g. K. pneumoniae)*, carbapenem resistance
- *Non-fermentative gram-negative bacteria (e.g. Pseudomonas aeruginosa)*, carbapenem resistance

Dr Monnet concluded that we are facing a shift in the trends of resistance threats. While resistance levels in gram-positive bacteria, in particular MRSA, are still high in many areas and pose a substantial health treat, the increasing resistance curves for these pathogens seem to flatten, and the sum of cases of common, antibiotic-resistant gram-positive bacteria (mostly MRSA and vancomycin-resistant *E. faecium*) is now comparable to that of common, antibiotic-resistant gram-negative bacteria (third generation cephalosporin-resistant *E. coli* and *K. pneumoniae*, and carbapenem-resistant *P. aeruginosa*). Thus, we are facing a steady rise in levels of resistance among gram-negatives, in particular in bacteria-producing extended spectrum betalactamases (ESBL) for which the treatment options are extremely limited.

Overall, it was estimated that in 2007 approximately 25 000 patients died from an infection due to any of five selected antibiotic-resistant bacteria (MRSA, VRE, ESBL-producing *E.coli* and *K. pneumoniae* and carbapenem resistant *P. aeruginosa*) in the European Union, Iceland and Norway. In addition, infections due to any of the selected antibiotic-resistant bacteria resulted in approximately 2.5 million extra hospital days and extra in-hospital costs of more than EUR 900 million. Overall, the cost to society as a result of infections due to the selected antibiotic-resistant bacteria was estimated at about EUR 1.5 billion each year. Dr Monnet pointed out that there are many reasons (e.g. limited range of included bacteria, outpatient infections not being considered, average cost of hospital care which does not take into account special patient care such as intensive care) to support a conclusion that these figures represent an underestimation of the human and economic burden of infections due to antibiotic-resistant bacteria.

Dr Bo Aronsson from the European Medicines Agency (EMEA) highlighted the current status in the research and development pipeline of antibacterial agents. By reviewing two large commercial databases, it was possible to identify which antibacterial agents are currently in clinical development worldwide. Whenever possible, agents identified by the search were assessed for their antibacterial activity against the selected bacteria based on actual data available in the databases or in the literature. In the absence of actual *in vitro* data, reviewers also took into account reasonable assumptions of the likely activity of some agents based on the properties of the antibiotic class or of the mechanism of action involved, thus constructing a 'best-case scenario'. Additionally, for each agent, reviewers were requested to indicate whether it acted on the same target as that of previously licensed antibacterial agents, or whether it acted through a new mechanism of action.

The main results from this analysis were as follows:
- Of 90 antibacterial agents identified by the searches, there were only 27 agents with in vitro activity in a best-case scenario against at least one organism in the panel of bacteria selected for their public health importance and assessed as having either a new target or a new mechanism of action, thus potentially offering a benefit over existing antibiotics.
- Of these 27 agents, there were 15 that

could be systemically administered and of these, only eight were judged to have activity against at least one of the selected gram-negative bacteria.
- Of the eight with activity against gram-negative bacteria, four had activity based on actual data and four had assumed activity.
- Of the four with activity against gram-negative bacteria based on actual data, two acted on new or possibly new targets and none via new mechanisms of action.

Dr Aronsson also stressed that there is currently no new agent against problematic gram-negative bacteria in clinical confirmatory trials. It will take several years for a new drug to reach the market.

4. Policies and incentives for promoting innovation in antibiotic research

Professor Elias Mossialos, London School of Economics and Political Science

The Swedish Government has commissioned the European Observatory on Health Systems and Policies to investigate the situation regarding the lack of effective antibiotics active against resistant bacteria. The scientists responsible for the report were Professor Elias Mossialos and a team of collaborators at the LSE.

This comprehensive report also includes a review of possible ways to give fresh stimulus to the antibiotics market through economic and regulatory means. This was a major objective of the conference and was addressed in detail by the conference workshop entitled *Financial and legislative options*, which brought together experts from the relevant fields of regulation, policy and economics.

Antibiotics are different from most other drugs in that, in time, the therapeutic effects will inevitably decrease due to resistance. To minimise the speed of this development, there is a need to reserve these products for patients who need them in line with strict and rational criteria. As expressed in economic language, there are two externalities related to antibiotic use. An externality is an effect that is not directly caused by the economic transaction, in this case selling and buying the antibiotic, but that follows as a consequence for a third party. The obvious positive externality is the cure of the infection which is beneficial for the patient and society. The other obvious, but negative, externality is the possibility of triggering resistance which lessens the value of the merchandise. One can probably add other externalities as well, e.g. those associated with adverse drug reactions and the negative environmental effects of the products.

Related to these externalities are some properties of the antibiotic market that are disincentives for the developers. Five such properties can easily be identified:

1. The existence of generic market competition from old off-patent drugs that may still be effective to varying degrees depending on the clinical circumstances.
2. Efforts to conserve existing antibiotics and preserve new products for future use, which slow down the market.
3. The limited duration of antibiotic therapy, which is often curative.
4. The propensity of developing resistance which limit use even before the patent/exclusivity has expired.
5. The influence of pricing and reimbursement.

These factors combined make the risk-adjusted net present value (NPV) – the estimated commercial potential of a product – about ten times less for an

antibiotic compared to a muscular-skeletal painkiller. Thus, "the greatest challenge is to persuade companies to invest in a market with low returns" compared to alternative investments.

Incentives to promote research and development in antibiotics

Incentives to encourage R&D are traditionally divided into two categories – push and pull mechanisms. Push mechanisms come in at an early stage to ease the start of R&D, mainly by offering grants, venture capital, (co)funding or other support that reduces the costs and risks of embarking on a promising project. Pull mechanisms are the carrot held some distance away offering a reward to the successful contender having reached certain pre-set goals. They could be simple monetary prizes, the promise of tax deductions or credits, intellectual property (market time) extensions or specified advanced market commitments (AMC). The latter means an agreed volume or value of the product being ordered once it is available. There are some advantages and disadvantages connected with each of these categories. Suffice to say that an obvious uncertainty of the pull mechanism is that rules may be changed over time and the fulfilment of such promises may depend on the politicians in office.

In order to maximise the benefit of the two approaches, Professor Mossialos advocates the application of product development partnership (PDP) and the call option for antibiotics models that are hybrids of the two basic approaches, push and pull. Hybrids will partially cover the developer's early R&D costs, and a profit will be made on the successful completion of the development chain. The prospect of profit is highly motivating and the risks are shared between the funder and the developer. One could well imagine that the existence of such a possibility may greatly influence whether the project is carried out or not.

The Call Options for Antibiotics (COA) model is a hybrid push mechanism that combines the principles of call options in equity markets with principles of AMC. A purchaser can buy a right during the drug development phase to purchase a specified amount of the drug at a later date for a specified price. If the drug fails, the purchaser will only have paid a premium equal to the cost of the initial option. The value of this option is expected to reflect the expected future profit from holding the option. This means scaling down the business risk taken by the purchaser and probably also introducing some profit if the initial value of the option was lower than the level of profits made when the drug came onto the market. Probably more important is that the developer may be motivated to start the project and bring it to a successful conclusion, thus making a new priority drug available to patients. As stated at the end of the report executive summary, "the COA model combines the financial investment incentives of an equity market and the clarity regarding minimum market size found in AMCs, with a 'light touch' public-private collaboration…"

Pricing and reimbursement

This area could also be used to increase the incentives for the development of prioritised antibiotics, but voluntary efforts would be required as the EU Member States each have their own national systems. An agreed and standardised European approach to assessments in this area could give a strong positive signal to the developers and providers of priority antibiotics. Even minor price restructuring within the EU may help to attract companies back to this therapeutic area.

5. Presentation of results from workshops on Innovative Incentives for Effective Antibacterials held on 16 September 2009.(For a summary of the workshop proceedings see the Annex.)

Workshop 1 *– Regulatory possibilities to enhance the development, approval procedure and availability of new antibacterials.*
The workshop was chaired by Dr Tomas Salmonson from the Medical Products Agency (MPA), Sweden. Dr Mair Powell from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK acted as rapporteur. The workshop involved 17 experts within the field representing e.g. regulatory agencies, academia and the pharmaceutical industry (EFPIA). The focus of the workshop was antibacterial agents for which a particular medical need exists, i.e. with activity against pathogens for which very few or none of the currently licensed drugs are effective. In addition, other more general regulatory issues regarding antibacterial agents were discussed.

Workshop 2 *– Financial and legal options*
The workshop was chaired by Dr Richard Laing from WHO. Rapporteur was Dr Chantal Morel from the London School of Economics and Political Science. The workshop involved 17 experts from governments, the European Commission, academia, the pharmaceutical industry (EFPIA), agencies for aid, reimbursement and regulatory agencies, the Pew Charitable Trust and Médecins sans frontières. The discussions were related to the report published by Professor Elias Mossialos and the London School of Economics and Political Science, *Policies and incentives for promoting innovation in antibiotic research*

Workshop 3 *– Research strategies towards new drug targets and compounds for treating bacterial infections as well as new diagnostic tools.*
The workshop was chaired by Professor Ragnar Norrby, former Director General of the Swedish Institute for Infectious Disease Control. Rapporteur was Dr Katarina Nordqvist, formerly of the Swedish Governmental Agency for Innovation Systems (VINNOVA). The workshop was assisted by a group of 18 experts representing the European Commission, governmental agencies, academia and medicine, large and small pharmaceutical companies, the healthcare sector and the charity sector. A broad review of present research strategies for the creation of innovative antibacterials and rapid diagnostic tools was carried out.

6. Views and perspectives of the pharmaceutical industry

Dr John Rex, AstraZeneca, representing EFPIA

The reasons for the difficulties for industry to develop new effective antibiotics were discussed. Besides the regulatory hurdles experienced by companies, it was acknowledged that finding new antibacterial drugs is surprisingly hard. This is particularly evident for gram-negative bacteria, especially non-fermenters, due to the cell wall composition and an array of various resistance mechanisms. New approaches such as antibodies, peptides, RNA inhibition and phage therapy have not yet delivered. Thus, it seems that proven modalities such as small molecules and, in some situations, vaccines are still the most plausible way forward. While it is relatively easy to find new targets, problems with physical properties and safety make it very difficult to develop a

drug-like compound. One major challenge is the fact that large, sustained research teams are needed. Many different skills are involved in this process and efforts must be sustained over several years. In order to succeed, suitable incentives would certainly be welcomed by the pharmaceutical industry.

Dr John Rex further stressed the need for new diagnostics, which are considered to be a very valuable tool. Effective diagnostics would be a way to alleviate the developmental process and could improve development economics. Even a moderately accurate diagnostic tool would enrich the trials with patients infected with key pathogens and reduce the sample size of confirmatory clinical studies, which would in turn reduce costs and time. Accurate diagnostics would also protect the utility of drugs over time.

Dr Rex concluded by stating that pharmaceutical firms cannot do this alone. Diagnostics and drugs are separate knowledge areas and businesses have not found them easy to combine. He suggested that IMI may represent a useful step forward in this field.

Anthony Man, MD FRCP, representing EFPIA
Antibacterials for resistant bugs – Can small companies afford the innovation risk?- A personal viewpoint.
Pharmaceutical companies with development programmes for antibiotics are becoming scarce because more costly data is required by the regulatory authorities. This will delay entry onto the market, and returns will be less while economic risk increases. A crucial limiting factor is the availability of operating capital until revenues come. Small companies would need incentives that reduce the innovation risk i.e. lower development costs, speedy entry onto the market, a "fair return" on investment and maintained revenue security. Also at the start of the product development phase, regulatory changes to enable fast approval and economic support in the form of grants/loans/fee waivers would be much appreciated. When the product is granted market authorisation, a price that reflects the medical value and faster reimbursement decisions are necessary. The time needed to be granted price and reimbursement status currently varies from less than 3 months to more than a year. Patent extensions/data exclusivity as well as tax credits would improve revenues during the life cycle of a product and thus make it more attractive to embark on the development of a product.

Small companies can afford the innovation risk if incentives help them to manage this risk.

7. Panel discussion

Dr Melinda Medgyaszai, State Secretary at the Hungarian Ministry of Health, emphasized the need for antibiotics in the healthcare panorama. She based this view on her personal professional experience as a microbiologist. She would not like to hand over a world where antibiotics do not work to her children and grandchildren.

Mr Göran Hägglund, Swedish Minister for Health and Social Affairs and host of the conference, stressed the importance of applying sufficiently forceful action from the very beginning of a process of change that will favour the development of new and much needed antibiotics. He is committed to continuing support, and intends to submit the suggestions to the Council for decision later this autumn. He considers this to be an important first step, but

the process has to continue with discussions with the relevant stakeholders.

Dr Dirk Cuypers, President of the Federal Public Service Health, Food Chain Safety and Environment in Belgium, promised to continue this work during the Belgian Presidency next year. From his point of view the different stages of drug development represented by research, discovery and clinical trials are of special interest, as are incentives in tax reduction. By managing a number of issues concerning the financing of drug development and later pricing, it would be possible to create a 'window' for the development of new drugs. Presently, Belgium allows a substantial 25 per cent increase in health costs for innovative drugs.

Mr Ivo Hartman, Director General for Economic and International Affairs in the Czech Republic, stressed the progress made by the recent Slovenian, French and Czech Presidencies on topics related to the treatment and prevention of infections. He also underlined the Czech interest in sustainable financial systems to support the development and use of needed drugs.

Ms Ruxandra Draghia-Akli, Director at the DG Research of the European Commission, stressed the need for more evidence-based research in the EU. She stated that, so far, more than EUR 200 million had been invested in research related to resistance to antibiotics. The Innovative Medicines Initiative is a joint partnership between the European Commission, the pharmaceutical industry and academia. Ms Draghia-Akli foresees the need for increased support from the Commission in this area. Today, there are many new possibilities to enter into collaboration and form partnerships with the aim of stimulating the development of innovative drugs.

Mr John F Ryan, Head of Unit at the DG Health and Consumer Protection of the European Commission, said it was necessary for future Presidencies to continue to bear the responsibility for this problematic area of global character. The prudent use of antibiotics and policies related to prescriptions and disease control are crucial. He would welcome reinforced prevention and education about how to treat infections related to healthcare institutions and continuing surveillance by the ECDC.

Mr Martin Terberger, Head of Unit at the DG Enterprise and Industry of the European Commission, believes that the present problem is very complex and that there is no quick fix available. He appreciates the fact that the report from the European Observatory does not come up with a patent solution. Suggestions to improve the situation have to be further worked on by stakeholders, civil servants and politicians.

Mr Thomas Lönngren, Executive Director of EMEA, expressed his view that two very useful days had been dedicated to this pressing priority. He commented that the use of antibiotics in animals had not been on the agenda. He was satisfied with the GAP analysis completed jointly by the EMEA and the ECDC and said it was an important document for making progress in the cause. The EMEA is continuously developing the regulatory aspects, which is in line with the EMEA mission to enhance the development of innovative drugs. Mr Lönngren will bring up the case of the deficient development of new antibiotics and market failure with his US counterpart at the FDA, at its regular bilateral meetings. Mr Lönngren also stated the need for a global approach in the area. Finally, Mr Lönngren compared the need for new effective antibiotics with other needs, e.g.

drugs for rare diseases, pediatric drugs and advanced therapies where legislative and organisational measures have been taken. A likely first step would be to designate prioritised antibiotics. This has been shown to stimulate applications for the approval of new drugs and facilitate their way through the regulatory system.

Dr Johan Giesecke, Deputy Head of the European Centre for Disease Control, confirmed that the phenomenon of increasing antimicrobial resistance is the highest priority for the ECDC and for Europe. He sees a discrepancy between the media and public interest and the seriousness of the steady increase in the frequency of antimicrobial resistance in some bacteria. The ECDC has made a valuable contribution to the GAP analysis by highlighting the serious and worrying nature of the facts presented in the analysis. Other important initiatives are the Antibiotic Awareness Day that is now held in the Member States and gives momentum to the necessary measures that have to be taken to turn around developments.

8. General discussion

Médecins sans frontières highlighted the problem of how innovative new, and thus supposedly expensive, medicines should be made available in low-income countries. The organisation believes that this problem was not sufficiently addressed at the conference, nor in the background material that was produced. The organisation's representative thought patients' needs should come first, and Médecins sans frontières "wants new ideas to steer and finance medical research and development, and ensure access to medicines".

The need for long-term commitment that would involve citizens and their MPs was emphasized. The threat of MDR bacteria has to be made clear to voters and politicians in order to bring about a change.

The question of price coordination in the EU was raised, but it was thought that these are matters subject to national decisions. It was suggested that within ongoing aid programmes involving substantial amounts of money, health aid and specifically the topic of fighting infections and the emergence of multidrug-resistant bacteria could be given higher priority. Other programmes for improving the availability of important drugs have relied on a combination of carrots and sticks, and have been successful. Given the right incentives, one can be hopeful that this will also be the case for new antibacterials.

Closing of the meeting

Mr Hägglund closed the meeting and agreed that there should be more awareness of the problem of antibacterial resistance, as it is a real threat that must be addressed if we are to make the future safer for our children. He feels a strong personal commitment to pursuing this issue and looks forward to the meeting of the EPSCO Council later this autumn when the Council conclusions can hopefully be adopted by the EU health ministers. Mr Hägglund cordially thanked everybody, including the moderator Mr Niklas Ekdal, who had contributed in different ways to the workshops and the conference.

Annex
Summary reports from Workshops held on September 16

Workshop 1 – regulatory possibilities to enhance the development, approval procedure and availability of new antibiotics

Introduction

This workshop considered the available regulatory mechanisms and current clinical data requirements in the EU for the initial approval of new antibacterial agents and for variations to add indications for use. The discussions focused on possible ways in which regulatory pathways could further facilitate and encourage the development and approval of new antibacterial agents and whether there is any scope for modification of the clinical data requirements.

The focus of the workshop was on antibacterial agents with potential for clinical efficacy against pathogens resistant to several or many licensed products, taking into account that these pathogens may still be uncommon or even rare so that accumulation of clinical experience in their treatment is often difficult to obtain. It was recognized that many of the issues discussed are also applicable to the development of new antibacterial agents to treat uncommon or rare types of infections and pathogens (regardless of their resistance patterns) due to the difficulties of obtaining clinical efficacy data to support specific claims for use.

Problem formulation

Pathogenic bacteria acquire resistance to each new antibacterial agent that is introduced to clinical practice. There is a constant need to develop new antibacterial agents with activity that is unaffected by as many bacterial mechanisms of resistance as possible. Since 2000 several new antibacterial agents have been approved in the EU, including some with clinical activity against certain multidrug-resistant Gram-positive organisms. However, only one of these new agents has activity against some multidrug-resistant Gram-negative organisms and this agent is not active against some organisms that are becoming problematical in the EU (e.g. carbapenem-resistant organisms).

The results of the joint EMEA/ECDC Gap Analysis have shown that several new agents currently in clinical development may have useful clinical activity against multidrug-resistant Gram-positive organisms (including MRSA and VRE). In contrast, very few are likely to be useful for treating infections due to Gram-negative pathogens that are resistant to one or many of the currently licensed agents. Multidrug-resistant Gram-negative organisms (e.g. including those that are resistant to carbapenems, fluoroquinolones and aminoglycosides) are increasing in frequency in the EU and worldwide. They commonly occur in severely ill patients with underlying conditions and pose very major difficulties for patient management. A European and global strategy to address this gap is urgently needed.

Pharmaceutical companies are increasingly reluctant to invest in antibacterial drug discovery and clinical research for reasons that include, but are not limited to, relatively low returns on investment compared to several other therapeutic areas and the need to conduct specific studies to support individual indications for use. Long and expensive clinical development programs are an unattractive prospect. If a new active substance shows in-vitro activity against multidrug-resistant organisms the low frequency of some

of these pathogens makes it very difficult or impossible to amass sufficient cases to unequivocally demonstrate clinical efficacy. Even if such an antibacterial agent is approved for one or more major indications in reality it is likely to be used only to treat infections known or suspected to be due to multidrug-resistant pathogens so the market is small. For these and many other reasons several companies have abandoned antibacterial drug development.

It is important that the available drug regulatory procedures and data requirements should encourage the clinical development of new antibacterial agents as far as is possible. EU Regulators are very aware of the problems posed to clinical practice by the increasing frequency of infections caused by drug-resistant pathogens including some for which there are few remaining therapeutic options. The CHMP guideline on the development of antibacterial agents includes a consideration of the clinical evaluation of new antibacterial agents with in-vitro activity against drug-resistant pathogens, including multidrug-resistant organisms. The clinical data requirements suggested in the guideline are intended to facilitate the approval of antibacterial agents that demonstrate clinical efficacy against drug-resistant pathogens as early as possible during the overall development program.

Drug regulation is designed to protect the Public Health. A balance must be achieved between making new effective therapies available as soon as possible and the generation of a pre-licensure safety database that is sufficient to support a conclusion of a favorable benefit-risk relationship for each of the intended indications for use. For antibacterial agents the extent of the safety database that would be required before first approval takes into account the intended indications for use and the patient populations (e.g. with serious and life-threatening infections) so that relatively small databases might be acceptable for agents shown to have clinical activity against pathogens for which treatment options are limited.

Details of suggested proposals

The term *drug-resistant pathogen* in the following sections refers to:

- Pathogens that demonstrate resistance to agents from several different classes of antibacterial agents (i.e. which may be called multidrug-resistant pathogens) and to
- Pathogens that demonstrate resistance to only one or a few types of antibacterial agents that results in a significant limitation of the therapeutic options.

• EU guidance allows for possible approval for use against drug-resistant pathogens based on limited data (e.g. 10-20 treated cases or even less). As always the acceptance of limited safety and efficacy data will be viewed in light of the overall benefit-risk relationship, which will take into account the intended indications for use. That is, if the target pathogens are very likely to cause life-threatening infections the clinical context of the benefit-risk relationship is different compared to some other situations.

• Efficacy data for drug-resistant pathogens can be generated in small numbers during large indication-specific studies or in small targeted studies or both. When numbers are expected to be small, randomized underpowered studies are preferred over uncontrolled studies (including those that employ external or historical controls, in which case the

former are preferred). However, it is acknowledged that uncontrolled studies are sometimes unavoidable. Therefore there is flexibility in acceptable study designs.

• PK/PD is already accepted to partly or wholly replace dose regimen selection, although its ability to predict the duration of treatment is still limited. PK/PD analyses are not accepted to replace efficacy data with the sole exception of infections/pathogens for which it is truly impossible to obtain clinical data (e.g. inhalational anthrax). PK/PD analyses can provide support for use of an antibacterial agent when it is possible to accumulate only very limited clinical data. For example, when the in-vitro and PK/PD data suggest efficacy against a particular pathogen but clinical studies are able to provide efficacy on only a relatively small numbers of cases.

The field continues to advance and it may be possible to place more weight on PK/PD analyses when designing studies and determining the extent of clinical efficacy data that may be required. For example, it may ultimately be possible that PK/PD analyses could support extrapolation of efficacy demonstrated in studies in one indication to use for other indications.

Meanwhile the assessment of PK/PD relationships during efficacy studies is encouraged. Obtaining PK/PD assessments from test and control groups could enhance the assessment of non-inferiority based on clinical and microbiological endpoints and add robustness to the conclusions.

• With the exception of new agents that may have only a very narrow spectrum of activity, initial applications for approval and additions of indications should be supported by a safety database of sufficient size to allow for an adequate assessment of benefit-risk in the indications sought. In the last decade several new antibacterial agents have been approved for single initial indications with relatively small safety databases.

• Pooling of data on drug-resistant pathogens across studies in the same indication is possible. It is also possible to pool efficacy data across studies of infections at same/similar body sites (e.g. IAI + pelvic; CAP + HAP).

• Studies in which any patient infected with a particular drug-resistant pathogen, wherever the site of infection, are enrolled are not currently encouraged and unqualified pathogen-specific indications are not currently accepted by EU Regulators. It was suggested that one possible approach to evaluating the clinical efficacy of new antibacterial agents with activity against rare multidrug-resistant pathogens might be to enroll patients with serious infections due to specific pathogens regardless of the known or suspected primary focus. This would then have to be reflected in a pathogen-specific indication. No consensus was reached but it was suggested that the possibility be revisited by the CHMP and its SAG.

• The development of rapid diagnostic tests that could enhance the enrolment and assessment of patients infected with certain pathogens and/or pathogens with specific mechanisms of resistance could greatly contribute to the provision of efficacy data.

• It is proposed that eligibility criteria should be developed to identify antibacterial agents suitable for special designation based on expectation of clinical activity against drug-resistant pathogens. The exact criteria should be developed in accordance with outcomes of other workshops. The eligibility criteria should reflect current and anticipated problematic drug resistance, which could be updated regularly in conjunction with ECDC and EMEA, so that the criteria are updated at regular intervals as seems appropriate.

• Following granting of this special designation it is proposed that scientific advice should be free of charge. These requests for CHMP scientific advice that concern the provision of data on safety and efficacy in small numbers of cases caused by resistant pathogens should be considered by a standing drafting sub-group of the SAWP. An early appointment of Rapporteurs would assist in providing continuity of the regulatory approach.

• The wording of the indications granted might need to differ from the usual CHMP approach since it may be necessary to mention specific organisms in 4.1 in order to accurately reflect the clinical data. An early discussion with EU Regulators of how the results of the planned clinical studies might be reflected in the SPC is not routinely part of scientific advice requests. However, this could be helpful since it could also influence the design of confirmatory efficacy studies. Alternatively or in addition a more clear method of reflecting efficacy against resistant pathogens in section 5.1 of the SPC would be helpful. This is already under consideration in the draft revision of the guideline.

• The revision of the guideline on clinical development of antibacterial agents should outline a clear pathway for approval of antibacterial agents. As far as is possible in light of scientific developments CHMP advice should be in accordance with the guideline and special consideration should be given to adherence to past advice unless exceptional circumstances arise.

• Conditional approval is a possible regulatory mechanism open for use although it may not always be necessary. This may be accompanied by a framework for rolling review and accelerated final assessment.

• With regard to the specific obligations that would accompany Conditional approval it is not feasible to obtain interpretable additional data on efficacy against drug-resistant pathogens in the post-approval period. The collection of data on treated cases due to specific drug-resistant pathogens in observational studies will likely be of very limited use because the patients with these types of infections commonly have a complicated clinical course and underlying problems that make the interpretation of the data extremely difficult.

However, a Conditional approval based on limited safety data with specific obligations to conduct post-approval safety observational studies could be a way forward. This might not be applicable if the pre-clinical data or the existing safety data raised issues that indicated the need for further safety data to be obtained. Conditional approval and

full approval is routinely accompanied by commitments to monitor resistance to the new agent and to report at intervals.

• Enrolment of patients into clinical studies targeted to enroll patients infected with drug-resistant pathogens might be facilitated if it was allowed to obtain informed consent before a patient enters a period of known risk for acquisition of such organisms e.g. prior to iatrogenic neutropenia or prior to an expected post-operative period in an ICU.

• There are some special considerations for Paediatric Investigation Plans (PIPs) when it is possible to generate only very limited data in adults. Formulation of a model plan regarding data requirements for children in these types of scenarios could assist in product development. Obtaining data on nosocomial multidrug-resistant pathogens from children, including neonates, in ICUs might supplement the data obtained in adults.

• The preparation of age-appropriate formulations suitable for children may meet issues regarding meeting quality standards. For example, use of specific excipients. Some general consideration of such issues by the QWP of the CHMP might assist in the development of appropriate formulations.

• There is already some considerable degree of harmony with respect to EU and US regulatory requirements. Harmonization of requirements with regard to developing agents that may be suitable for treating drug-resistant pathogens would be useful. This is an issue that could be taken up by the pharmaceutical industry.

Synthesis and discussion

The existing EU regulatory procedures and data requirements already allow for some degree of flexibility in study designs and data requirements. Suggestions were made for:

- Keeping EU data requirements under review as advances are made in various fields and in accordance with the properties of the new antibacterial agents reaching clinical development.

- How PK/PD analyses could support limited clinical efficacy data and enhance the comparisons that are made between the test and comparative agents.
- Further exploration of how the existing EU mechanisms and regulations could be better used to facilitate early approval of new antibacterial agents. In particular:

• To establish a new designation for certain antibacterial agents with potential clinical efficacy against certain types of drug-resistant pathogens. Such designation could be accompanied by free access to CHMP scientific advice, early appointment of Rapporteurs, rolling review of data and an accelerated final assessment of the application dossier.

• These agents may receive full or conditional approval depending on the available data. Conditional approval based on limited efficacy data could be accompanied by obligations to conduct well-designed post-approval observational safety studies provided that the non-clinical and available clinical data do not point to any specific risk.

• There may be scope for using a small drafting group to assist the CHMP's SAWP with scientific advice for all antibacterial agents, including those that have met the designation criteria.

• An early discussion of how the clinical data might be reflected in sections 4.1 and 5.1 of the SPC could assist in design of the clinical development program. For example, the prescribing information should make it clear if the agent has been shown to have clinical efficacy against drug-resistant pathogens and, as necessary, explain the limitations of the data.

Concluding statements

The 2004 CHMP guideline on the clinical development of antibacterial agents included provisions that were intended to facilitate and encourage antibacterial drug development and to minimize delay in initial approvals. The ongoing 2009 revision of the document will continue to allow flexibility with respect to clinical data requirements.

A major outcome of this workshop was to propose that criteria should be developed for determining the eligibility of new antibacterial agents for a special designation category based on their potential clinical efficacy against drug-resistant pathogens. The designation could be accompanied by free access to CHMP scientific advice, early appointment of Rapporteurs, rolling review of data and an accelerated assessment of the application dossier resulting in full or conditional approval depending on the available data. If initial approval is based on limited safety data there could be a specific obligation under conditional approval to conduct post-approval observational studies.

While this workshop focused on specific issues for the development of antibacterial agents with activity against drug-resistant pathogens it was discussed that there is also a need to encourage Companies to enter or stay in antibacterial drug development. Detailed attention to how this might be accomplished was outside the scope of the workshop but it was recognized that there is a need for further discussions on this matter. These issues could be discussed and addressed during the finalization of the revision of the CHMP antibacterials guideline

Workshop 2 – financial and legislative options

Introduction & Background

Each year an estimated 2 million patients in the EU incur hospital-acquired infections such as methicillin-resistant *Staphylococcus aureus* (MRSA). Of these patients an estimated 175,000 will die as a result of the infection[1]. The growing number of bacteria-related deaths being seen across Europe is a result of our current arsenal of antibiotics becoming increasingly obsolete in the face of rising levels of resistance to virulent pathogens. If we continue to use antibiotics in the way in which we have become accustomed, without developing new ones, antibiotic treatment will soon no longer be effective. Eventually the decreasing efficacy of these drugs will also begin to counteract the advances achieved in medical care more broadly. For example, advanced surgical procedures and cancer chemotherapy will become more dangerous to perform without the necessary complementary antibacterial treatment. Over time many of the advances we've made in modern medical practice over the past several decades could be negated, undoubtedly with an immense human toll. Faced with the high likelihood of a resistance-triggered impending health crisis, a European strategy to address the lack of new antibiotics – based on the best available evidence – is badly needed. This narrow window of opportunity must not be foregone.

Problem formulation

Why don't we have effective antibiotics?

- High levels of resistance against many existing drugs
- Limited investment in developing new drugs

Why are so few companies investing in antibiotics?

Antibiotics are not an attractive area for pharmaceutical companies for the following reasons:

1. Resistance to antibiotics is a biological consequence to their use. Conservation efforts to protect existing antibiotics intended for severe infection entail limiting their consumption, which limits the size of the potential market.
2. The chance of resistance occurring over the patented life of the antibiotic lowers expected returns on investment.
3. The limited duration of antibiotic regimes, along with their fully curative nature (as opposed to simply mitigating symptoms as in the case of chronic diseases) decreases expected returns on investment. Relative to markets in other therapeutic areas the antibiotics market does not appear as offering comparable returns.
4. The prioritization and corresponding price paid by public purchasers does not reflect the relative effectiveness of antibiotics in reducing morbidity and mortality.
5. Developing antibiotics with new mechanisms of action presents a high level of risk to the potential developer

[1] European Academics Scientific Advisory Council (EASAC). Tackling Antibiotic Resistance in Europe. 2007.

Details of suggested proposition

What can we do to prevent a complete health disaster?

1. Monitor resistance to all antibiotics
2. Implement strong infection control measures in all health care settings (especially hospitals)
3. Invest and promote the use of rapid, point-of-care diagnostics that can be used within all levels of care (including within primary care)
4. Ensure that all financing and performance-related incentives for health practitioners support the rational use of effective antibiotics
5. Invest in the development of novel antibiotics with new mechanisms of action to slow the growth of resistance

What can we do to support the development of new, effective antibiotics?

1. We can invest money to help pay for inputs in the development process (push mechanisms). Examples include:
   - Training of researchers
   - Support basic research through grants and fellowships
   - Offer research-related tax incentives
   - Implement and partially fund product development partnerships with industry
   - Support collaborative and open-source approaches
   - Low-interest bridging loans

2. We can create incentives that mimic a functioning antibiotics market to lure developers (pull mechanisms). Examples include:
   - Advance Market commitments
   - Prizes with or without patent buyout
   - Extended intellectual property protection
   - Re-evaluation of current national pricing and reimbursement mechanisms
   - Review of regulatory processes to facilitate market entry

Synthesis and discussion

It is increasingly clear that neither push nor pull incentives will suffice. Push incentives alone are likely to help steer early research in the desired direction, however, they will not be strong enough to lure the necessary level of investment and activity to bring a sufficient number of new products to market. Pull incentives alone impose too much risk on developers and exclude all potential developers lacking access to enormous capital or to a sufficiently large existing drug portfolio to cross-subsidize the development of the new antibiotic. If we are to promote the development of effective new antibiotics in a sufficiently expedient and equitable manner we will need to use both push and pull incentive mechanisms.

Appropriate design of the incentive package is essential. An optimal incentive package would:

1. Spread risk between the developer and the funder
2. Limit rewards to true innovation
3. Maintain uncomplicated partnerships between the funder and developer
4. Discourage over-marketing or over-consumption
5. Consider eventual access to the product globally through market segmentation (e.g. between rich and poor countries) by way of full or at least partial decoupling of price from the recouping of developer investment costs
6. Address bottlenecks in the value chain of R&D, whether scientific or financial
7. Attract SMEs as well as larger companies to take on this challenge

Concluding statements

After careful consideration of numerous incentives the Working Group on Financial and Legislative Incentives recommends the following:

- The high potential for an impending health crisis along with the high cost of resistance to existing antibiotics is justification for public action
- An incentive package combining both push and pull elements should be implemented on a European level with long-term earmarked funding, isolated from economic and budgetary fluctuations
- Development of appropriate diagnostics should become a priority
- National level pricing and reimbursement systems should align drug prices to their therapeutic value
- Further research should be conducted into key areas to increase the viability of effective antibiotics in the future (e.g. fixed-dose combinations, alignment of prescriber performance and financing-related incentives to support rational prescribing and consumption)
- A widely representative group of stakeholders including ministries of finance, science, economic affairs, development, regulatory affairs, price and reimbursement agencies, industry, investment community, consumer and patient groups, patent and antitrust lawyers, and legal authorities should be convened to further develop the course of action
- The priority of this initiative should be carried forward by the Commission through the upcoming Presidencies to ensure that concerted action is taken and followed through

Workshop 3 – Survey Research Strategies Towards New Drug Targets and Compound for Treating Bacterial Infections as well as new Diagnostics

1. Introduction & Background

Resistance to antibiotics is a rapidly growing global problem. Each year, more than 25 000 patients die in the EU from an infection with multidrug-resistant bacteria. Already today the bacterial infection scenery is alarming, for example:

- Some common infections, such as urinary tract infections in otherwise healthy patients, are caused by multi-resistant bacteria, against which no pharmaceuticals in tablet form are effective.
- Infections have arisen in intensive care caused by bacteria for which no effective treatment is available.
- Patients with multi-resistant bacteria must be isolated in order to reduce the risk of spread to other patients. This entails high additional costs for the health care system.

Overall, infections due to antibiotic-resistant bacteria result in extra healthcare cost and productivity losses of at least EUR 1.5 billion each year in the EU.

2. Problem formulation

In parallel with the increasing burden of bacterial resistance, there are very few antibacterial agents with new mechanisms of action under clinical development to meet the challenge of multidrug resistance. The reasons for this could be several, e.g., insufficient research activities to exploit the numerous available novel antibacterial targets, very high development costs and uncertainty about market value for new substances.
There is a particular lack of new agents against infections caused by multi-drug-resistant Gram-negative bacteria. Only two agents with new or possibly new targets and documented activity were identified in the gap report by the ECDC/EMEA ("The bacterial challenge: time to react"). Both agents were in early phase of clinical development.
In the diagnostic field there is a need for rapid, point-of-care identification of bacterial aetiology of infections. This is true both for patients with mild or moderate infections in out-patients settings and for hospitalised patients with severe infections. There is also a lack of methods for rapid detection of antibiotic resistance. Such diagnostic methods would allow a reduction of antibiotic usage and facilitate the choice of effective drugs.

Analyses of research and patent activities show that the number of scientific articles published in the antibacterial field has increased during the past 10 years, while patent applications have remained constant (VINNOVA report, "Bad Bugs-Future Drugs?"). The report shows that the development of basic research has not been followed up by patent applications. There may be several reasons for this, such as the research that is published being at too early a stage for a patent application, that companies have changed their patenting strategies and apply for patents at a later stage of development, that companies find it difficult or risky to develop new compounds or diagnostics, and that the potential economic rewards are insufficiently attractive for the companies.

To address both current medical needs and future emergence of new resistant pathogens, a European and global strategy that facilitate the innovation system for the development of new antibacterial medicinal products and diagnostics is urgently needed.

3. Synthesis of discussion

The objective of workshop 3 was to review new drug targets and other possibilities to get new antibacterial products or treatment options, as well as innovative strategies for rapid diagnosis of bacterial aetiology as well as fast detection of antibiotic susceptibility.

Issues that were discussed:

- Does antibiotic therapy remain as the main therapeutic option to treat infections including those caused by resistant strains?
- Target and drug screening problems?
- Which alternative strategies to the classical antibiotic concept are worth pursuing?
- Which diagnostic means are needed to accomplish a limited and narrower antibiotic therapy?
- Rapid diagnostics?
- Where in the innovations system do we have the main hurdles?
- What is needed now? Within 5-15 years? Longer perspective?

4. Details of suggested propositions

The problem with increasing antibiotic resistance and lack of new antibacterial pharmaceuticals must be addressed in several ways.

Task Forces

To deepen and maintain the dialogue between the government, the health care systems, academia, industry and relevant authorities, task forces at national and EU levels should be established. They should include representatives from all relevant ministries, industry, universities and health care systems.

Research

For successful development of innovations based on current research, increased interaction between basic research and clinical research, with a clear coupling to patient needs, will be needed. It is therefore important, for a positive development of research within the antibacterial field that the area is given priority for research funding at both national, EU and global levels.

Suggested research areas for future funding were;

- Innovative medicinal chemistry and screening
- Host-pathogen interactions
- Models for predicting future resistance trends
- Improved tools for predictive toxicology
- New diagnostics
- Health economics (burden of antibiotic resistance)

Public Private Partnerships

Initiative should also be taken at national, EU and global level to establish public private partnership/programmes, in order to stimulate collaborations required for development of innovations that can supplement current antibiotics. Academia, health care systems, authorities and industry may in this way be brought together in order to develop basic research projects in the antibacterial field towards new innovations, both in diagnostics and in pharmaceuticals.

Specific possible approaches would be the creation of an antibiotic innovation fund, possibly modelled from the Wellcome Trust Seeding Drug Discovery Initiative, SDDI and make further use of the Innovative Medicines Initiative.

5. Concluding statements

- **Create task forces on national and EU level against antibiotic resistance. To deepen and maintain the dialogue between the government, health care systems, academia, industry and relevant authorities. Such task forces should deal with continued surveillance of antibiotic resistance as well as means to reduce the resistance problems including incentives for innovations.**

- **Ensure, both at national, EU and global levels that resources are available for continued research initiatives in the antibacterial field, including basic research, clinical research and the needs of patients.**

- **Initiate, at national, EU and global level, proactive public private programmes/partnership between academia, the health and medical care system, authorities and industry for the development of diagnostics and pharmaceuticals within the antibacterial field.**

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[2] The contents of the workshop reports do not necessarily reflect a common view shared by all participants but rather the scope of the discussions. The participants have expressed themselves in their personal capacities and not as official representatives of their respective organizations

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