



Transatlantic Taskforce on Antimicrobial Resistance

**Recommendations for future collaboration
between the U.S. and EU**

2011

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Executive summary

Antimicrobial resistance, or the ability of microorganisms to withstand treatment with drugs to which they were once susceptible, is a significant and multifaceted public health problem. In addition, the scarcity of new antimicrobial agents and the dearth of new agents in the drug development pipeline limit treatment options, particularly for patients with infections caused by multidrug-resistant (MDR) organisms. The societal and financial costs of treating antimicrobial-resistant infections place a significant human and economic burden on society, as individuals infected with drug-resistant organisms are more likely to remain in the hospital for a longer period of time and to have a poor prognosis.

In response to the mounting threat of antimicrobial resistance, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established by Presidential declaration in 2009 at the annual summit between the EU and US presidencies. The purpose of the taskforce is to identify urgent antimicrobial resistance issues that could be better addressed by intensified cooperation between the US and the EU within the following key areas:

1. Appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities;
2. Prevention of both healthcare- and community-associated drug-resistant infections;
3. Strategies for improving the pipeline of new antimicrobial drugs.

Through regular meetings and several public consultations, the members of the TATFAR have identified a set of 17 recommendations in these key areas where future cooperation would prove fruitful. Each recommendation is explained in detail, along with timelines for implementation and appropriate implementers in the Recommendations section. A summary of the recommendations can be found below.

Upon adoption of the recommendations contained in this document, the TATFAR intends to begin the process of implementation. The TATFAR would oversee the proposed activities for a period of two years to ensure that implementation is carried out.

TATFAR recommendations for future collaboration

I. Appropriate therapeutic use in human and veterinary medicine

| Opportunity for collaboration | Recommendation |
|---|---|
| Antimicrobial stewardship in human medicine | Develop common structure and process indicators for hospital antimicrobial stewardship programmes |
| Surveillance of antimicrobial use in human and veterinary communities | Convene a joint EU/US working group to propose standards for measuring antimicrobial use in hospital settings |
| | Collaborate in collection of data on sales and use of veterinary antimicrobials in food-producing animals |
| Risk analysis on foodborne antimicrobial resistance | Collaborate on implementation of the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance prepared by Codex Alimentarius |
| | Enhance information sharing on approaches to promoting appropriate use in veterinary communities |
| Campaigns to promote appropriate use in human medicine | Establish an EU–US working group to assess the evidence for effectiveness of communications tools in promoting behaviour change to increase appropriate use and to develop joint priorities |

II. Prevention of drug-resistant infections

| | |
|---------------------------------|--|
| Surveillance of drug resistance | Consultation and collaboration on a point-prevalence survey for healthcare-associated infections (HAIs) |
| | Develop a process for transatlantic communication of critical events that may signify new resistance trends with global public health implications |
| | Encourage efforts to harmonise, to the extent possible, epidemiological interpretive criteria for susceptibility reporting of bacterial isolates across surveillance programmes in the US and EU |
| Prevention strategies | Convene a workshop bringing together public health experts from the US and EU to develop consensus evaluation tools for hospital infection control programmes |
| | Develop a transatlantic strategy to facilitate vaccine development for HAIs |

III. Strategies for improving the pipeline of new antimicrobial drugs

| | |
|--|--|
| Incentives to stimulate the development of new antibacterial drugs in human medicine | Policymakers should strongly consider the establishment of significant incentives to stimulate antibacterial drug development |
| Research to support the development of new antibacterials | Increase communication between US and EU research agencies to identify common scientific challenges that may represent opportunities for collaboration |
| | Publicise funding opportunities to EU, US research communities |
| Regulatory approaches for antibacterial products | FDA and EMA intend to discuss ways to facilitate the use of the same clinical development programme to satisfy regulatory submissions to both Agencies |
| | Establish regular meetings between FDA and EMA to discuss common issues in antibacterial drug development and regulation |
| | Exchange information on possible approaches to drug development for bacterial diseases where limited drugs are available |

Introduction

History and scope of the antimicrobial resistance problem

The introduction of penicillin in the 1940s led to a dramatic reduction in illness and death from infectious diseases. However, penicillin-resistant bacteria were isolated from patients soon after the drug was introduced. Since then, numerous new antimicrobial agents have become available, many of which have been rendered ineffective by the remarkable ability of bacteria to become resistant via mutation or acquisition of resistance genes from other organisms. When an antimicrobial drug is used, the selective pressure exerted by the drug favours the growth of organisms that are resistant to the drug's action. The extensive use of antimicrobials has resulted in drug resistance that threatens to reverse the tremendous life-saving power of these drugs.

Antimicrobial resistance is not a new phenomenon; however, the current magnitude of the problem and the speed with which new resistance phenotypes have emerged elevates the public health significance of this issue. As a result, only 70 years after their introduction, we are facing the possibility of a future without effective antibiotics for some infections – a future where operations and treatments such as cancer chemotherapy and organ transplants could become more dangerous. In addition, the scarcity of new antimicrobial agents and the dearth of new agents in the drug development pipeline limit treatment options, particularly for patients with infections caused by multidrug-resistant (MDR) organisms, which occur mainly in healthcare settings. The societal and financial costs of treating antimicrobial-resistant infections place a significant burden on society – a burden that is likely to grow as the number of drug-resistant infections increases. Individuals infected with drug-resistant organisms are more likely to remain in the hospital for a longer period of time and to have a poor prognosis. No studies or surveys have been conducted in both the US and the EU that use similar methods, patient populations and bacteria, making comparisons of the impact of antimicrobial resistance between the two continents difficult. Studies on deaths attributable to a small and differing selection of MDR infections show that, each year, these infections result in an estimated 25 000 deaths in 29 countries in Europe (5.1 per 100 000 inhabitants) and 12 000 deaths in the US (4.0 per 100 000 inhabitants)^{1,2}. If all MDR infections and other infections with problematic resistance profiles were included in these studies, the estimate of deaths would be inarguably higher. The history and scope of the resistance problem has been reviewed extensively elsewhere^{1,3}.

There has been a steady decline in the number of new antibacterial drugs entering the market place over the last few decades on both sides of the Atlantic^{1,3,4}. In the setting of continued development of antimicrobial resistance and an insufficient pipeline to supply new options, the problem of antimicrobial resistance has become more pronounced. Because of the time and expense required to bring a new compound from the point of discovery to the market place, it is important to respond to the current situation and to prepare for the future. The goal of such efforts is to ensure that effective treatments are available to treat patients with serious infectious diseases including patients with resistant organisms. The recent recognition of the NDM-1 genotype of resistance in certain Gram-negative bacteria⁵ reminds us that the biology of resistance will continue to evolve and has the capacity to significantly impact our ability to treat infections.

In addition to their central role in human medicine, antimicrobials have been used extensively in livestock and poultry since their discovery for the treatment, control and prevention of animal diseases, as well as for production purposes (e.g. to enhance growth, improve feed efficiency). In contrast to human medicine where treatment is typically directed at a single patient, entire groups of animals may be treated by the use of medicated feed and/or water. As a result of continued exposure to antimicrobials, the prevalence of resistant bacteria in the faecal flora of food animals may be relatively high. Determining the impact of these resistant bacteria on the management of human infections is an ongoing challenge as many classes of antimicrobials used in food-producing animals have analogues to human therapeutics and are therefore capable of selecting for similar resistance phenotypes. Of note, a number of these antimicrobial agents are also used in companion animal medicine and aquaculture (fish production).

Developing new drugs alone will not be sufficient to address the growing resistance problem. Microbes will always find a way to escape the harmful actions of new drugs – therefore it is essential to preserve the efficacy of existing drugs. Promoting the appropriate use of antimicrobial agents – use which maximises therapeutic effect while minimising the development of antimicrobial resistance – in both human and veterinary medicine is key to reducing selective pressure that leads to the development of resistance. Vaccination represents one of the best tools we have to control the spread of infectious diseases and their associated resistance factors. New vaccines for bacteria with threatening resistance profiles (e.g. *Staphylococcus aureus*, *Clostridium difficile*, *Pseudomonas aeruginosa*) could help to stem the emergence and spread of resistance in these pathogens. Another way to decrease selective pressure on bacteria in the gut and the environment is to use drugs with a narrow spectrum of activity. This type of targeted treatment will remain limited until

¹ ECDC/EMA Joint Technical Report: [The bacterial challenge: time to react](#), 2009.

² Zell BL, Goldmann DA. *Infect Control Hosp Epidemiol*. 2007 Mar;28(3):261-4.

³ Boucher, HW et al. 2009. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. *Clin Infect Dis* 48(1): 1-12

⁴ Mossialos E, Morel C, Edwards S, Berenson J, Gemmill-Toyama M, Brogan D. Policies and incentives for promoting innovation in antibiotic research. London: London School of Economics and Political Science; Available from: http://www.se2009.eu/polopoly_fs/1.16814!menu/standard/file/LSE-ABIF-Final.pdf. September 2009.

⁵ Walsh T et al. *Int J Antimicrob Agents*. 2010, Suppl 3: S3-14.

new rapid diagnostic tests for invasive bacterial infections are developed. In addition, rapid diagnostics have the potential to facilitate the clinical development of drugs by allowing efficient identification of eligible patients.

Establishment of the Transatlantic Taskforce on Antimicrobial Resistance

The growing global threat of antimicrobial resistance was recognised by US President Obama, Swedish Prime Minister and then-European Council President Reinfeldt, and European Commission President Barroso at the 2009 US–EU summit. The summit declaration called for the establishment of “a transatlantic taskforce on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us.” The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was constituted based on this declaration.

Composition of the TATFAR

In order to launch its work immediately, membership of the TATFAR was restricted to US government employees and EU civil servants. Nine members from each side of the Atlantic were selected based on the areas of expertise identified in the summit declaration. A roster of the TATFAR members can be found in Annex G.

Scope of the TATFAR

Antimicrobial resistance is a diverse issue with numerous contributing factors. The work of the TATFAR primarily focused on the specific areas identified in the summit declaration.

Working structure of the TATFAR

The primary task of the TATFAR was to define specific areas where enhanced EU–US cooperation could have the most significant impact. To accomplish this, three working groups, corresponding to the three key areas identified in the summit declaration were formed (see Annex C).

1. Appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities
2. Prevention of drug-resistant infections
3. Strategies for improving the pipeline of new antimicrobial drugs and diagnostic devices and maintaining existing drugs on the market

TATFAR public consultations

Recognising the importance of antimicrobial resistance to a wide range of stakeholders, TATFAR organised several public consultations to solicit input. These comments were carefully considered by the working groups when formulating the recommendations presented in this report.

Stakeholder consultations included:

- US: stakeholder listening session, 7 June 2010, Washington, DC
- US: public consultation and associated web-based solicitation, 1 October 2010, Bethesda, MD
- EU: web-based consultation, November–December 2010

A summary of the comments received during these sessions can be found in Annex F.

During these public consultations, some stakeholders recommended that TATFAR address the threat of antimicrobial resistance on a global scale. Although this recommendation is beyond its scope, the TATFAR agrees with the importance of addressing antimicrobial resistance in developing countries, in addition to developed ones. The World Health Organization (WHO), Codex Alimentarius, the World Organisation for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO) have developed a series of key international initiatives addressing antimicrobial resistance at the international level in the field of veterinary medicine. However, similar initiatives and leadership from organisations such as WHO are urgently needed in the field of human medicine. Members of the TATFAR feel that strengthened cooperation under the umbrella of the WHO is the most appropriate means to address this increasing public health threat on a global scale.

Recommendations

1. Appropriate therapeutic use of antimicrobial drugs in human and veterinary medicine

Background

Antimicrobial drugs are critical to human and veterinary health. However, since their employment contributes to the emergence of drug-resistant organisms, these essential drugs must be used appropriately in human and veterinary medicine to avoid use that unnecessarily adds to resistance development without benefit to human or animal health.

Studies indicate that nearly 50% of antimicrobial use in hospitals is unnecessary or inappropriate⁶. There is no doubt that this overuse of antibiotics is contributing to the growing challenges posed by *Clostridium difficile* and other antibiotic-resistant bacteria in many hospitals. Studies also demonstrate that improving the use of antibiotics in hospitals can not only help reduce rates of *Clostridium difficile* infection and antibiotic resistance, but can also improve individual patient outcomes while substantially reducing healthcare costs⁷. Likewise, recent studies suggest that outpatient prescribers continue to prescribe antibacterials for acute respiratory infections, most of which are caused by viruses. In a 2009 EU-wide survey, 53% of Europeans believed that antibiotics kill viruses and 47% believed that they are effective against colds and the flu⁸; therefore patient expectations may contribute to overprescribing in outpatient settings. Furthermore, a recent study found an upward trend in the use of broad spectrum antimicrobials to treat acute respiratory infections where narrow-spectrum drugs are recommended⁹. To combat this problem, antimicrobial stewardship programmes and campaigns to promote adherence to them are critical to preserving the effectiveness of existing antimicrobials. Both the US Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) are active in these key areas; see Annex E for detailed descriptions of ongoing programmes.

Questions regarding the impact of antimicrobial drug use in food-producing animals have been raised and debated for many years. A variety of scientific committees, taskforces, and organisations have studied and published on the matter, beginning with the Swann Report in 1969. In 1997, the WHO published the first of several reports on this issue, The Medical Impact of Antimicrobial Use in Food Animals¹⁰. In 2000, a WHO expert consultation resulted in WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food¹¹. During the same time period, many reports on the topic were published by European and American scientists and deliberative bodies as well as by government agencies. Three recommendations appear repeatedly in the reports, including: enhanced monitoring of resistance among bacteria from food animals and food of animal origin; promoting the responsible use of antimicrobials; and requiring the use of antimicrobials in animals be prescribed by veterinarians.

Both the EU and the US have been involved in international work on antimicrobial resistance in Codex Alimentarius, the World Health Organization and the World Organisation for Animal Health (OIE), but bilateral joint activities are limited. Several national or regional activities related to a variety of relevant issues, including legal provisions, research, animal health programmes, education of animal health professionals, marketing authorisation provisions of antimicrobial veterinary medicinal products, prudent use guidelines, surveillance of AMR and antimicrobial use, diagnostic development, and off-label use have taken place.

Opportunities for collaboration

➤ Antimicrobial stewardship in human medicine

Appropriate use of antimicrobials drugs is essential to minimise selective pressure and preserve effectiveness of these dwindling agents. To this end, many hospitals have implemented antimicrobial stewardship programmes, which may include guidelines for appropriate drug selection, dosing, route of administration and duration of antimicrobial therapy. However, specific components of stewardship programmes vary widely.

Issue: A common way to assess antimicrobial stewardship programmes is needed

Recommendation 1: Develop common structure and process indicators for hospital antimicrobial stewardship programmes

⁶ Dellit T et al. Clin Infect Dis (2007) 44(2):159-177.

⁷ Kallen A et al. Infect Control Hops Epidemiol (2009) 30(3):264-72.

⁸ http://ec.europa.eu/health/antimicrobial_resistance/docs/ebs_338_en.pdf

⁹ Kronman M et al. Pediatrics (2011) 127;3, 411-417.

¹⁰ <http://whqlibdoc.who.int/hq/1997/WHO EMC ZOO 97.4.pdf>

¹¹ http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSRAPH_2000.4.pdf

CDC and ECDC plan to share US and EU methods for evaluating hospital antimicrobial stewardship programmes. If resources permit, a meeting of subject matter experts would be convened to review scientific evidence supporting indicators of antimicrobial stewardship programme implementation and effectiveness. If there is consensus among members of this expert group, they would propose an evidence-based strategy for the use, monitoring and interpretation of structure and process indicators that would include a minimum set of indicators that could be validly included in US and EU country strategies to allow comparisons among institutions and regions.

- Implementers: CDC, ECDC and other stakeholders
- Timeline: two to three years from adoption of recommendation

➤ Surveillance of antimicrobial use in human and veterinary communities

To promote appropriate use of antimicrobials, the quantity and quality of antimicrobial use in diverse settings must be measured and analysed. However, different countries and user communities have different standards for measuring antimicrobial usage.

Issue: Methods to measure antimicrobial use in hospitals vary widely, preventing data comparison

Recommendation 2: Convene a joint US/EU working group to propose standards for measuring antimicrobial use in hospital settings

Much of the human antimicrobial use occurs in healthcare settings and surveillance activities to measure antimicrobial use in these settings are underway at both ECDC and CDC with the purpose of using these data to improve antimicrobial use. The potential impact of these data increases if the data collected in the EU and in the US can be compared. This would require synchronising data sources and methodology (i.e. numerator) to generate a common metric or measures that can easily be compared (e.g. defined daily dose [DDD], days of therapy [DOT], etc.). Resources permitting, an EU/US expert working group would be convened to identify the steps needed to synchronise methodology or produce comparable data.

- Implementers: CDC, ECDC and other stakeholders
- Timeline: Two to three years from adoption of recommendation

Issue: Common measures of antimicrobial use in veterinary medicine are needed in order to compare data between the US and EU and follow trends over time across sectors and regions

Recommendation 3: Collaborate on collection of data on sales and use of veterinary antimicrobials in food producing animals

The US and EU should work closely with the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) and OIE to achieve this goal. The work would also address the development of common units of measurement of antimicrobial drug use that are needed for the further analysis and comparison of the data. Preferably, data collection should allow stratification by product type, to allow efficient prioritisation of control measurements. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project could serve as an opportunity to share experience on such data collection. A long-term goal of this work would be to lay the foundation for methods to interpret the information in relation to antimicrobial resistance data in the US and EU and to explore the link between use of antimicrobials and the development of resistance.

- Implementers: FDA, EFSA and EMA
- Timeline: Two to three years from adoption of recommendation

➤ Risk analysis of food-borne antimicrobial resistance

Issue: Methods for analysing the risk of antimicrobial resistance in foodborne pathogens vary widely

Recommendation 4: Collaborate on implementation of the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance prepared by Codex Alimentarius

The Codex Alimentarius Ad Hoc Intergovernmental Taskforce on Antimicrobial Resistance produced a draft set of guidelines for risk analysis of foodborne antimicrobial resistance to be adopted in 2011. If resources permit, a forum would be created for working in parallel or jointly on antimicrobial resistance risk analysis to promote consistency between the US and the EU in implementing the internationally accepted guidelines.

In relation to this recommendation, an area of particular concern in both the EU and US is the 'extra/off-label' use of antimicrobials, particularly those critically important to human health, in food-producing animals. Working together on

risk analysis of extra/off-label use, where data are available, may be particularly valuable in developing risk management measures appropriate for each region.

- Implementers: FDA, EFSA, EMA, and DG SANCO
- Timeline: one to two years from adoption of recommendation

Issue: Methods to promote appropriate use of antimicrobials in veterinary communities vary in the US and in EU Member States

Recommendation 5: Enhance information sharing on approaches to promoting appropriate use in veterinary communities

The TATFAR identified some further areas that may represent opportunities to learn from one another. These include: the European Surveillance on Veterinary Antimicrobial Consumption (ESVAC), various risk management measures to restrict certain uses of critically important antimicrobials as well as animal health programmes aiming to improve animal health in order to reduce the need to use antimicrobials. For more information on ongoing efforts to promote appropriate veterinary use in the US and EU, see Annex E.

- Implementers: EMA, DG SANCO, FDA, EFSA and other stakeholders
- Timeline: within two years of adoption of recommendation

➤ **Campaigns to promote appropriate use in human medicine**

Both the US and the EU have well-developed campaigns to promote appropriate use of antimicrobials. New or modified themes on appropriate antimicrobial use are created for annual events in November, during which organisations, governments and other interested groups use these themes to communicate about prudent use of antibiotics with specific groups (e.g. physicians, parents, general public).

Issue: Campaigns to promote appropriate antimicrobial use must be periodically updated based on effectiveness data and societal factors

Recommendation 6: Establish an EU–US working group to assess the evidence for effectiveness of communications tools in promoting behaviour change to increase appropriate use and to develop joint priorities

Effectiveness research is needed to improve the impact of appropriate antibiotic use campaigns and other behaviour change interventions at international, national and local levels and to ensure best use of limited resources. This could be aided by a joint group of experts from the US and EU, which could review existing evidence, propose changes in campaign components and indicate where more research would be helpful. This group could periodically publish a review of efforts to improve antibiotic use, including changes in knowledge by practitioners and improvement in institutional changes to ensure appropriate use.

Representatives from the US Get Smart Campaign and European Antibiotic Awareness Day intend to annually discuss the development of joint priorities for the focus of campaigns that would have greater impact if supported bilaterally. In addition, campaign materials for adaptation and use in national campaigns could be shared.

- Implementers: CDC and ECDC
- Timeline: Within two years of adoption of recommendation

2. Prevention of drug resistant infections

Background

The burden of healthcare-associated infections (HAIs) has increased over the past few decades due to the increase in immunocompromised and elderly patients, increasing use of invasive indwelling devices such as catheters, more complex hospital environments and inadequate infection control measures. Antimicrobial resistance has emerged in virtually all healthcare-associated (nosocomial) pathogens, and the majority of novel resistance factors first surface in healthcare facilities. Furthermore, resistant bacteria are also causing infections in the community with increasing frequency. Prevention of drug-resistant infections requires that the transmission of drug-resistant bacteria between individuals be interrupted. Surveillance is an important tool to identify populations where drug-resistant reservoirs and infections occur and to assess the effectiveness of infection control interventions to prevent the dissemination of the bacteria to new individuals and populations. In many cases, effective infection control interventions are known but implementation requires adequate training of healthcare professionals and educational campaigns for both healthcare professionals and the general public. In other cases, identifying effective infection control interventions requires additional research.

Opportunities for collaboration

➤ Surveillance of drug resistance

Prevention of healthcare-associated infections (HAIs) requires knowledge of HAI prevalence and characteristics (i.e. resistance profiles). Both CDC and ECDC conduct surveillance for infections caused by antimicrobial-resistant bacteria that may include collecting patient-level information as well as collecting and characterising the resistant bacterial isolate. These surveillance efforts differ in their objectives, the networks within which surveillance is performed, the platforms used to collect data and the data that are collected. Platforms such as the US National Healthcare Safety Network (NHSN) and the EU Healthcare-Associated Infections Network (HAI-Net) are useful, but in many cases data submission is voluntary and as such can be limited.

Issue: Methods for collecting information on Healthcare-Associated Infections (HAIs) vary widely

Recommendation 7: Consultation and collaboration on a point-prevalence survey for HAIs

ECDC and CDC have each embarked upon a point-prevalence study of HAIs that will provide national estimates of HAI rates and information about the epidemiology of infections. Although methodologies used in the two studies are not identical, ECDC and CDC developed the protocols after consultation with each other. The full-scale US survey will be conducted in 2011 and countries of the EU will complete their survey by the end of 2012. Upon completion, CDC and ECDC plans to hold a meeting to compare results, report high-level survey findings and identify approaches that are adaptable for future state-based or country-based surveillance efforts in the US, EU and elsewhere.

- Implementers: CDC and ECDC
- Timeline: Within three years of adoption of recommendation

Issue: Public health officials need to be kept informed of emerging resistance trends to be prepared to respond appropriately

Recommendation 8: Develop a process for transatlantic communication of critical events that may signify new resistance trends with global public health implications

Despite differences in surveillance systems, identifying critical surveillance results that require international communication and actions is important. A joint meeting of CDC and ECDC to identify criteria for antimicrobial resistance results that warrant transatlantic communication and to draft a preliminary communication protocol is proposed. The mechanisms should allow for timely communication and for proper dissemination of information within the US, EU and to partner public health agencies and ministries of health. These decisions should be consistent and complementary to US and EU efforts to collect critical antimicrobial resistance results at the local, state or country level.

- Implementers: CDC and ECDC
- Timeline: within two years of adoption of recommendation

Issue: Susceptibility criteria differ in the US and EU, making comparison of resistance rates difficult

Recommendation 9: Encourage efforts to harmonise, to the extent possible, epidemiological interpretive criteria for susceptibility reporting of bacterial isolates across surveillance programmes in the US and EU

The CLSI (Clinical Laboratory Standards Institute) and EUCAST (European Committee on Antimicrobial Susceptibility Testing) are non-governmental entities (with governmental representation) that establish interpretive criteria for susceptibility reporting of human, food and veterinary isolates in the US and EU, respectively. The TATFAR supports any collaborative efforts to work towards greater harmonisation of epidemiological interpretation of antimicrobial susceptibility results from surveillance programmes. The EU and the US plan to work with CLSI and EUCAST to convene a joint planning meeting in order to (1) identify the objectives of harmonisation and (2) identify any barriers or limitations for implementing harmonised criteria in ongoing surveillance systems.

This recommendation focuses solely on epidemiological interpretive criteria for susceptibility reporting, not for treatment purposes or clinical guidelines.

- Implementers: CDC, ECDC, EFSA, FDA, EU Member States, EU reference laboratory for antimicrobial resistance and other stakeholders
- Timeline: Within two years of adoption of recommendation

➤ Prevention strategies

Issue: Methods for the evaluation of hospital infection control programmes vary widely

Recommendation 10: Convene a workshop bringing together public health experts from the US and EU to develop consensus evaluation tools for hospital infection control programmes

Hospital infection control programmes are only effective if they are comprehensive and fully implemented. Each programme needs to be evaluated using structure and process indicators; however, standardisation of these evaluation tools is lacking. To promote consistent and thorough evaluations, public health experts from the US and EU intend to hold a workshop to establish consensus structure and process indicators for monitoring infection control programmes which are appropriate to the healthcare infrastructure of the US and EU countries and usable by other countries with or without modification.

- Implementers: CDC and ECDC
- Timeline: Within two years of adoption of recommendation

Issue: Surveillance data are needed to inform development strategies for vaccines targeting HAIs and to evaluate the impact of such vaccines after their introduction

Recommendation 11: Develop a transatlantic strategy to facilitate vaccine development for HAIs

Academic laboratories, small biotech companies and pharmaceutical companies, are developing candidate vaccines to prevent infection with common HAIs, including MRSA and *Clostridium difficile*. Such vaccines have the potential to significantly reduce the prevalence of antimicrobial-resistant infections and associated morbidity, mortality and costs. Identifying the appropriate target population(s) for such vaccines is challenging, and surveillance data have the potential to answer key questions about the best strategy for clinical testing of these products. Likewise, once such vaccines become available, surveillance data will be essential to assess effectiveness and impact. A working group of US and EU public health experts may be convened to identify areas where transatlantic collaboration would facilitate the identification of target populations and generation of cost-effectiveness data to enhance the attractiveness of these candidate products for commercial development.

- Implementers: CDC, ECDC and DG RTD
- Timeline: Two to three years from adoption of recommendation

3. Strategies to improve the pipeline of new antibacterial drugs for use in human medicine

Background

There are multiple scientific, regulatory and economic factors that are believed to have contributed to the decline in development of new antibacterial drugs. However, new antibacterial drug therapies are needed, and we can anticipate that the need will continue to grow in the future due to the emergence of new resistant bacteria that we cannot yet predict. Because developing a new drug takes time (typically 5-10 years), having a robust and diverse antibacterial drug pipeline is essential to be in position to treat patients' infections, both now and in the future.

Government agencies on both sides of the Atlantic recognise the critical need for new drugs to treat antimicrobial-resistant infections and are working to foster antibacterial research and development and to facilitate approval of new drugs through a variety of mechanisms. For example, both the US National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH), and the Directorate-General for Research and Innovation (DG RTD) at the European Commission have issued calls for proposals focused on the development of vaccines, drugs and rapid diagnostic tests for resistant pathogens of concern. In addition, NIAID/NIH offers a broad array of preclinical and clinical services designed to fill gaps in the drug development pipeline and lower the economic risk of antimicrobial drug development. At both the US Food and Drug Administration (FDA) and the EU European Medicines Agency (EMA) there has been considerable effort invested in the development of updated recommendations on the most appropriate clinical trial designs for the evaluation of antibacterial drugs. Several of these guidance documents were recently published and others are under development. Both groups are involved in regulation of the same types of, and often the same, products. In fact, the clinical trials that are conducted as part of a drug development programme are usually submitted to both regulatory authorities. More detailed descriptions of ongoing activities to stimulate the antibacterial drug development pipeline can be found in Annex E.

A number of factors contributing to the dwindling antibacterial drug development pipeline have been discussed extensively¹². Typical short courses of therapy, the seemingly inevitable emergence of resistance to new antibacterials, and a growing awareness of the importance of antimicrobial stewardship (an essential component in the public health response to resistance) are all issues that restrict the economic return on investment for antibacterial drugs. In addition, there are considerable challenges in performing clinical trials of a new antibacterial drug, many of which are a result of the biology of acute bacterial infections and their response to treatment. These factors include:

- Many patients with acute bacterial infections require urgent initiation of antibacterial drug treatment. Using current clinical care and clinical trial paradigms, it is difficult to quickly enroll a patient in a clinical trial to evaluate new antibacterial drug therapy.
- Prior non-study antibacterial drug therapy or concomitant antibacterial drug therapy may obscure the ability to assess the efficacy of the new antibacterial drug that is being tested.
- Current diagnostic methods often do not allow for immediate microbiological identification of the causative organism of a patient's infection at the time in which they should be enrolled in a clinical trial. For example, the disease may stem from a bacterial infection, a non-bacterial infection (e.g. viral) or a non-infectious cause. For a number of conditions, lack of accurate rapid diagnostic tests results in the need for larger clinical trials because only some patients will have a confirmed bacterial infection and can therefore be included in the analysis.
- In order to have a scientifically sound study, clinical trials may enroll patients with more severe disease, which can make studying an oral antibacterial drug more complicated because these patients may be too sick to take drugs orally.
- Changes in recommended clinical trial designs based on scientific advances have made the performance of these trials more difficult than in the past, adding to the economic risk of developing a new antibacterial drug.

These challenges are significant, but meeting them ensures that clinical trials of a new antibacterial drug are ethical and scientifically sound.

Opportunities for collaboration

➤ **Incentives to stimulate the development of new antibacterial drugs for use in human medicine**

A range of different types of mechanisms for providing incentives for antibacterial drug development have been discussed in publications on this topic and were the focus of several comments received during TATFAR public consultations. Some mechanisms are characterised as “push” mechanisms, such as funding for research to develop new antibacterial drugs, or “pull” mechanisms, such as rewards for successfully bringing a new antibacterial drug to market (e.g. longer exclusivity rights or patent terms). Incentives that reward appropriate use measures during the time that the drug is marketed have also been proposed. As noted below, a number of pre-clinical and clinical research resources are supported by NIH/NIAID and DG RTD to reduce research and development risks and costs; these are examples of “push” incentives already available to antibacterial drug developers.

Issue: New antibacterial drugs are needed now, but their development is inherently difficult due to the biology of these infections and potentially lower economic returns when compared with other therapeutic areas

Recommendation 12: Policymakers should strongly consider the establishment of significant incentives to stimulate antibacterial drug development.

There are complex economic issues involved in formulating a specific incentive programme to stimulate antibacterial drug development, such as determining the most effective type of incentive or mix of incentives. Because the development of incentives requires new legislation, TATFAR members are not in a position to advocate for any particular incentives programme. However, any new legislation should be developed with consideration of (1) ways of ensuring appropriate use of new antibacterials developed with public money, and (2) the feasibility of implementation by the relevant agencies. Given the global nature of drug development and potential international implications of incentives on drug development that may stretch beyond borders, EU and US TATFAR participants plan to keep each other informed should new incentives become available in either jurisdiction.

➤ **Research to support the development of new antibacterials**

Both the US and EU are targeting key areas to aid the development of novel therapeutics and to improve the use of existing ones. NIH/NIAID and DG RTD utilise an array of mechanisms to support antibacterial drug discovery and development at basic, translational and clinical stages. Details about the relevant funding mechanism from both agencies

¹² Mossialos E, Morel C, Edwards S, Berenson J, Gemmill-Toyama M, Brogan D. Policies and incentives for promoting innovation in antibiotic research. London: London School of Economics and Political Science; Available from: http://www.se2009.eu/polopoly_fs/1.16814!menu/standard/file/LSE-ABIF-Final.pdf. September 2009.

are included in Annex E. This section focuses on potential areas for collaboration that might benefit antibacterial drug development research.

Issue: Antimicrobial resistance research is a rapidly moving field with global implications

Recommendation 13: Increase communication between US and EU research agencies to identify common scientific challenges that may represent opportunities for collaboration.

Biomedical research is an increasingly global enterprise. It is imperative that funding agencies and the scientific community be aware of research findings and opportunities in other parts of the world. To this end, staff from NIH/NIAID and DG RTD plan to hold annual consultations to share progress within their research portfolios and potential future areas of research interest. In addition, NIH/NIAID and DG RTD proposed to bring together relevant scientific communities to discuss scientific hurdles and regulatory standards in the following key areas:

- **Diagnostics for invasive bacterial infections:** Rapid diagnostic tests for bacterial infections have significant potential to aid the clinical development of novel antibacterials. Over the past decade, both the EU and US have targeted the development of diagnostics for invasive bacterial infections and resistant subtypes in multiple calls for proposals (see Annex E for more details). However, this field still lags behind advances in the detection of viral and mycobacterial pathogens. A joint US–EU workshop could add great value if focused on specific scientific challenges and regulatory standards, as well as on the broader policy aspects of implementing new diagnostic tests in the clinical environment.
- **Rational use trials on both sides of the Atlantic:** Both the US and the EU are funding clinical trials to define optimal use of existing antimicrobial drugs in disease areas with the most antimicrobial selective pressure (see Annex E for more details). Investigators from the US and EU should be brought together to share their experiences and establish collaborations.
 - Implementers: NIH/NIAID and DG RTD
 - Timeline: within one year of adoption of recommendation

Issue: Investigators should consider funding sources and research resources on both sides of the Atlantic to support antimicrobial research and antibacterial product development efforts

Recommendation 14: Publicise funding opportunities to the EU and US research communities

Both the NIH/NIAID and DG RTD have a variety of funding opportunities available of which investigators on the other side of the Atlantic may not be aware. Enhanced visibility of these resources would enable funding of the best research projects and candidate products. Therefore, the working group agreed that existing resources, such as the TATFAR website and international research conferences should be leveraged to publicise these funding opportunities. A brief list of relevant activities is listed here. More details can be found in Annex E:

- **NIH/NIAID**
 - Investigator-initiated grant opportunities
 - Partnership programme for product development – targeted, milestone-driven translational research grants
 - Preclinical and clinical resources for researchers – services available to the research community with appropriate preliminary data
 - 'Omics services for researchers – services available to the research community
 - Requests for applications and proposals supporting specific initiatives
- **DG RTD**
 - Annual calls for transnational collaborative research proposals under the Seventh Framework Programme for Research and Development – antimicrobial resistance is a major priority area
 - Individual research grants awarded by the European Research Council (ERC)
 - Innovative Medicine Initiative (IMI) – a public-private partnership supporting pre-competitive research for faster discovery and development of new drugs
 - EUREKA's Eurostars Programme – aims to stimulate Small and Medium Enterprises (SMEs) to lead international collaborative research and innovation projects.
 - Implementers: NIH/NIAID and DG RTD
 - Timeline: within one year of adoption of recommendation

➤ Regulatory approaches for antibacterial products

FDA and EMA both recognise the importance of coordinating the requirements for clinical trials to support regulatory approval of new antibacterial drugs whenever possible. However, there are some differences between EMA and FDA, particularly in the area of non-inferiority trial designs – or studies designed to show that a new drug does not result in worse outcomes than an approved therapy by more than a defined margin – for some serious infections. The EMA and FDA may take different approaches when assessing available data and determining non-inferiority margins and endpoints for antibacterial drugs trials. The FDA has been revising guidance documents that provide recommendations on trial designs that are in compliance with FDA statute, regulation and policy^{13,14,15}. This work is in part in response to a series of inquiries regarding how the FDA was using non-inferiority trials to evaluate drug effectiveness, particularly in the area of antibacterial drugs¹⁶.

Issue: Antibacterial drug development programmes that satisfy regulatory requirements in both the US and EU could facilitate antibacterial drug development

Recommendation 15: FDA and EMA plan to discuss ways to facilitate the use of the same clinical development programme to satisfy regulatory submissions to both Agencies

Both EMA and FDA agree it is acceptable for a trial to have separate pre-specified statistical analysis plans that would evaluate different primary endpoints and/or would evaluate endpoints at different time points in accordance with the recommendations of both regulatory authorities. In certain instances, this should make it possible to utilise the same trial to meet the requirements of both regulatory authorities in those instances where the recommendations for the primary endpoint or the time of assessment are different.

- Implementers: FDA and EMA
- Timeline: within one year of adoption of recommendation

Issue: Enhanced communication between FDA and EMA on issues such as product review and emerging drug safety issues could be beneficial

Recommendation 16: Establish regular meetings between FDA and EMA to discuss common issues in the area of antibacterial drug development and regulation

The FDA and EMA regularly discuss issues of mutual interest under existing confidentiality agreements. Given the common areas of regulatory responsibility and the multinational nature of drug development, establishment of regular meetings could benefit regulators on both sides of the Atlantic and the field of antibacterial drug development as a whole. Exchanges should provide for sharing of scientific information, including information on products currently under review, clinical trial design issues and antibacterial drug safety issues

- Implementers: FDA and EMA
- Timeline: within one year of adoption of recommendation

Issue: Antibacterial drug developers need clear guidance on the development of drugs with the potential to treat resistant bacterial infections

Recommendation 17: Exchange information on possible approaches to drug development for bacterial diseases where limited drugs are available (i.e. bacterial diseases where there is unmet need because there are insufficient antibacterial drug therapies available, often due to the development of antimicrobial resistance)

Regulatory pathways for new drugs, specifically for multidrug-resistant infections, are currently under discussion at both EMA and FDA. Regular information sharing between FDA and EMA regarding scientific and regulatory approaches (e.g. clinical trial designs) can inform the advice that EMA and FDA provide to companies choosing to develop products for a bacterial disease where there is unmet need. In particular, discussions would be targeted towards development programmes for new antibacterial agents and guidance documents on the topic of developing drugs for bacterial disease in areas of unmet need.

- Implementers: FDA and EMA
- Timeline: within one year of adoption of recommendation

¹³ See United States Federal Food Drug and Cosmetic Act.

¹⁴ See 21CFR 314.126. Available from http://edocket.access.gpo.gov/cfr_2010/aprqr/pdf/21cfr314.126.pdf

¹⁵ See Guidance for Industry. Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070951.pdf>

¹⁶ United States Government Accountability Office, New Drug Approval: FDA's Consideration of Evidence from Certain Clinical Trials (GAO 10-798). July 2010. Available from: <http://www.gao.gov/new.items/d10798.pdf>

Strategies for maintaining antimicrobial drugs on the market was identified in the Terms of Reference as an area for exploration by the TATFAR. During discussions by the TATFAR, it became evident that there are several factors specific to the EU and its Member States that make this issue and its contributing factors different in the EU and the US. Such factors include: national formulary decisions by EU Member States, mechanisms of healthcare delivery, differing business decisions made by pharmaceutical companies across EU Member States, and differing patterns of antimicrobial resistance across EU Member States. After further understanding the nature of the factors involved and the differences between the EU and the US, the TATFAR decided that this would not be a fruitful area for transatlantic collaboration.

Conclusions and next steps

In this report, the TATFAR has identified a set of recommendations to strengthen EU and US communication and cooperation in the area of antimicrobial resistance that would entail further activities involving EU and US agencies. In order to ensure that these recommendations are transformed into concrete actions, the TATFAR recommends extension of its mandate for two additional years following the endorsement of the proposed recommendations by the EU and US leaders. During this time, the TATFAR intends to monitor the implementation of the recommendations via biannual audioconferences and, at the end of the two year extension, to hold a face-to-face meeting to review progress and consider potential next steps.

Annexes

Annex A – Abbreviations and acronyms

| | |
|------------------|--|
| AGISAR | WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance |
| AMR | Antimicrobial resistance |
| CLSI | Clinical Laboratory Standards Institute |
| DDD | Defined daily dose |
| DOT | Days of therapy |
| DG RTD | European Commission's Directorate-General for Research and Innovation |
| DG SANCO | European Commission's Directorate-General for Health and Consumers |
| CDC | US Centers for Disease Control and Prevention |
| EC | European Commission |
| ECDC | European Centre for Disease Prevention and Control |
| EFSA | European Food Safety Authority |
| EMA | European Medicines Agency |
| ERC | European Research Council |
| ESVAC | European Surveillance of Veterinary Antimicrobial Consumption |
| EU | European Union |
| EUCAST | European Committee on Antimicrobial Susceptibility Testing |
| FAO | Food and Agriculture Organization of the United Nations |
| FDA | US Food and Drug Administration |
| HAI | Healthcare-associated infection |
| HHS | US Department of Health and Human Services |
| IMI | Innovative Medicines Initiative |
| MDR | Multidrug resistant |
| MRSA | Methicillin-resistant <i>Staphylococcus aureus</i> |
| NDM-1 | New Delhi metallo-beta-lactamase 1 |
| NHSN | US National Healthcare Safety Network |
| NIH/NIAID | US National Institutes of Health / National Institute of Allergy and Infectious Diseases |
| OIE | World Organisation for Animal Health |
| TATFAR | Transatlantic Taskforce on Antimicrobial Resistance |
| US | United States of America |
| WHO | World Health Organization |

Annex B – 2009 EU-US Summit Declaration 3 November 2009

We, the leaders of the European Union and the United States, met in Washington to renew our global partnership and to set a course for enhanced cooperation that will address bilateral, regional and global challenges based on our shared values of freedom, democracy, respect for international law, human rights and the rule of law. Our goal is to ensure a more prosperous, healthy and secure future for our 800 million citizens and for the world. We will build upon our strong partnership and work together to strengthen multilateral cooperation. As the EU strengthens as a global actor, we welcome the opportunity to broaden our work together, particularly in the areas of freedom, security and justice.

The European Union and the United States economies make up over half of global GDP, account for over one third of world trade and are the leading providers of development assistance. The direct impact of our economic policies on the global economy has never been more apparent than over the past year, making the imperative of collaboration even greater. We recognize the importance of expanding our cooperation on issues of global concern, notably climate change, development, energy, cyber security and health. We therefore agree:

[...]

- To establish a transatlantic taskforce on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us.

[...]

Full text available at:

http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/er/110929.pdf

Annex C – Terms of reference

Objectives and outcome

The taskforce should increase the mutual understanding of US and EU activities and programmes relating to antimicrobial issues, deepen the transatlantic dialogue, provide opportunities to learn from each other, and promote information exchange, coordination and cooperation between the US and the EU.

The outcome of the taskforce efforts will be a proposal with suggestions for areas of future collaboration between the EU and the US. The proposal will be presented at the EU–US Summit in 2011, leaving it for the political leaders to decide on which initiatives should be approved and prioritised for further cooperation.

The challenges posed by antimicrobial resistance are well documented and one more report describing the current situation and the risks posed by antimicrobial resistance would not be the best use of the taskforce's limited time and resources. Therefore, the taskforce will not duplicate what is being done in other fora. The outcome of the taskforce should be regarded exclusively as technical and scientific statements or suggestions and neither represent or impose a formal or binding position on the part of the US or the EU.

Composition of the taskforce

The taskforce and any related working groups shall be composed of members of the civil service for the EU and government officials for the US. The members shall have a general overview on health-related issues or a specific knowledge on antimicrobial resistance. The taskforce will consist of 18 members (up to nine from the US and up to nine from the EU) and the secretariat.

The United States will be represented by the following agencies or offices of the Department of Health and Human Services:

- Office of Global Health Affairs (OGHA)
- Centers for Disease Control and Prevention (CDC)
- Food and Drug Administration (FDA)
- National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIH/NIAID)

The European Union will be represented by the following agencies and organisations:

- European Commission:
 - EC Directorate-General for Health and Consumers (two representatives)
 - EC Directorate-General for Research
 - European Centre for Disease Prevention and Control (ECDC)
 - European Medicines Agency (EMA)
 - European Food Safety Authority (EFSA)
- Council of the European Union, represented by the TRIO Presidency (Spain, Belgium, Hungary) in order to keep the Council regularly informed of progress.

Focus areas

The work of the taskforce will be guided by the focus areas defined by the 2009 EU–US Summit declaration "to establish a transatlantic taskforce on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us":

1. Appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities
2. Prevention of drug-resistant infections
3. Strategies for improving the pipeline of new antimicrobial drugs, diagnostic procedures and techniques, and maintaining existing drugs on the market

The taskforce will aim to conclude its work by March 2011, but may continue beyond this timeframe with the consent of all parties.

Operating procedures

The taskforce will be co-chaired by the US and the EU. The chairs will be appointed by consensus. The ECDC will provide the taskforce with a secretariat to deal with the administrative aspects of organising and running the day-to-day arrangements.

The work will be conducted in three distinct phases: (1) agreement between the EU and the US on the Terms of reference; (2) identification of potential issues for cooperation; and (3) drafting and discussion of the final document.

The taskforce will hold two face-to-face meetings. A kick-off meeting will be held in the US to agree on the Terms of reference, a timeline, appointment of the chairs of the taskforce and how to consult and involve third parties. A final seminar will be held in the EU in spring 2011, prior to the EU–US Summit, to provide orientation to the final report.

Consultation, external interaction and workshops

The US and EU partners of the taskforce will be seeking, where appropriate, to obtain input from the public, interested experts and other stakeholders, in accordance with each partner's respective process for obtaining public comment, on the specific activities within the framework of the Declaration where EU–US collaboration could be most fruitful.

Annex D – Timeline

Based on the terms of references, the EU and US TATFAR members agreed on the following timeline:

Public consultations

The EU and US to finalise their public consultation before the end of 2010.

Working groups

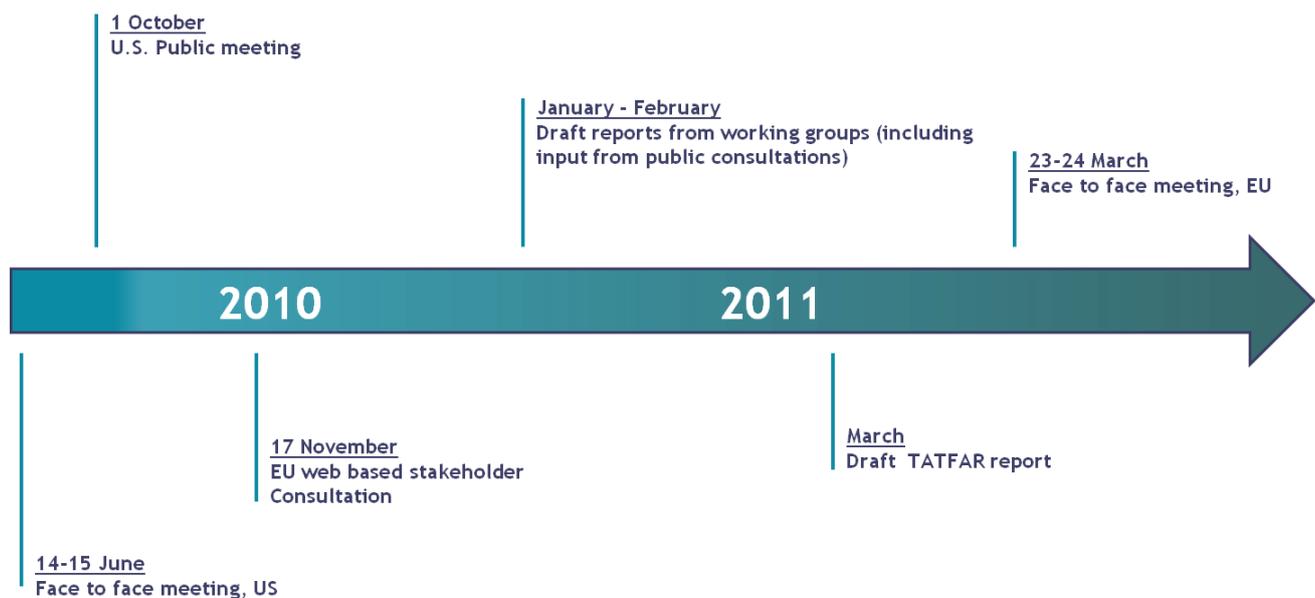
Each working group to provide:

- an interim report by the end of December 2010; and
- a final report by the end of January 2011.

TATFAR report

Based on these contributions:

- Drafting of the proposed TATFAR report in February and March 2011;
- TATFAR report adopted by consensus in March 2011.



Annex E – Ongoing activities: joint, EU and US

Note that this list of activities is not meant to be an exhaustive list of all activities undertaken by either the EU or the US to address antimicrobial resistance. The emphasis is on those major activities that could potentially provide opportunities to learn from each other, point to areas of future collaboration, or are either novel or highly successful projects. For more information on current activities to address the issue of antibacterial resistance, please see the respective websites of the relevant EU and American organisations and agencies.

1. *Appropriate therapeutic use of antibacterial drugs in the medical and veterinary communities*

➤ **Ongoing activities addressing appropriate therapeutic use of antibacterial drugs in medical communities**

A. Measures to support appropriate therapeutic use (of antibacterial agents) in medical communities

Antibacterial stewardship programmes

Joint activities

- Awareness campaigns on the prudent use of antibacterial agents in outpatient settings are supported in the US and the EU. The US campaign [Get Smart: Know When Antibiotics Work](#) is coordinated by CDC and the EU campaign [European Antibiotic Awareness Day](#) is coordinated by ECDC. CDC and ECDC are working closely to coordinate the campaigns. In 2010, the US and EU agreed to match the timing of their campaign launches (US: week of 18 November; EU: 18 November).

EU activities

- [European Antibiotic Awareness Day](#) is an annual European public health initiative that takes place on 18 November to raise awareness about the threat to public health of antibiotic resistance and prudent antibiotic use. The objective of the European Antibiotic Awareness Day in 2010 was to support efforts at national level to reduce unnecessary antibiotic use in hospitals through the development and dissemination of educational materials promoting prudent antibiotic use.
- [ABS \(AntiBiotic Strategies\) International](#) was a project to implement strategies for appropriate use of antibiotics in hospitals in Member States of the European Union. It was funded 2006–2008 and was a partnership of nine Member States of the EU: Austria, Belgium, Czech Republic, Italy, Germany, Hungary, Poland, Slovakia and Slovenia. It developed training and guidance documents on strategies, organisation, and structure and process indicators for hospital antimicrobial stewardship programmes.
- [CHAMP](#) (Changing behaviour of health care professionals and the general public towards a more prudent use of antimicrobial agents) is a project that summarised the available evidence and assessed expert opinions and views of professionals and patients on activities that aim at a rational and cost-effective use of antibiotic management of respiratory infections in primary care. Analyses of the cost-effectiveness of the different interventions that aim to improve antibiotic use has been performed. Based on the information that was gathered and analysed, a best-practice intervention has been developed. The project studied the implementation and feasibility of this best-practice intervention.
- [SATURN](#) (Specific antibiotic therapies on the prevalence of human host resistant bacteria) is a project that aims to study the impact of antibiotic exposure on antibiotic resistance with a multidisciplinary approach that bridges molecular, epidemiological, clinical and pharmacological research. Many results drawn from previous studies of the effect of antibiotic use on emergence, selection and spread of antimicrobial resistance have lacked a holistic view combining all aspects into one study. As part of SATURN, clinical studies will be conducted including a randomised trial to resolve an issue of high controversy (antibiotic cycling vs. mixing) and three observational studies on the effect of antibiotic use on antibiotic resistance that are not easily assessable through randomised trials.
- ECDC is preparing systematic reviews and evidence-based guidance on peri-operative antimicrobial prophylaxis, organisation of antimicrobial stewardship programmes and organisation of hospital infection control programmes. These are being developed during 2010–2013 and will include evidence-based guidance, structure and process indicators as well as implementation toolkits, where appropriate.

US activities

- [Get Smart for Healthcare](#) is CDC campaign focused on improving in-patient antimicrobial use. The goal of Get Smart for Healthcare is to optimise the use of antimicrobial agents in in-patient healthcare settings by focusing on strategies to help hospitals and other in-patient facilities implement interventions to improve antibiotic use. Interventions and programmes designed to improve antibiotic use are also referred to as “antimicrobial stewardship”. Some of the initial work of this effort includes: evaluating ways to improve the treatment of UTI, evaluating the epidemiology of in-patient antibiotic use, pilot testing the implementation of a novel stewardship implementation framework using the “Change Package and Driver Diagram Methodology” in partnership with the [Institute for Healthcare Improvement](#). Get Smart for Healthcare is currently targeted towards acute care hospitals and will expand to long-term care facilities.
- [Get Smart: Know When Antibiotics Work](#) was launched by CDC as the National Campaign for Appropriate Antibiotic Use in the Community in 1995. In 2003, this programme was renamed Get Smart: Know When Antibiotics Work in conjunction with the launch of a national media campaign. This campaign aims to reduce the rate of rise of antibiotic resistance by: promoting adherence to appropriate prescribing guidelines among providers, decreasing demand for antibiotics for viral upper respiratory infections among healthy adults and parents of young children, and increasing adherence to prescribed antibiotics for upper respiratory infections.

Appropriate use of diagnostic tests

EU activities

- [GRACE](#) (Genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections in Europe) is a Network of Excellence focusing on community-acquired lower respiratory tract infections (LRTI). The objective of GRACE is to integrate centres of research excellence and exploiting genomics in the investigation of community-acquired LRTI. Microbial and human genomics are being integrated with health sciences research consisting of clinical observational and intervention studies, health economics and health education to change practice in managing community-acquired LRTI. GRACE organised professional education, including web-based teaching and practical courses. GRACE created a genomic laboratory network in eight European countries and a primary care research network in 11 European countries. The consortium will become a virtual “European LRTI Research Centre”, potentially leading to a forum promoting research and good practice in the field of community-acquired LRTI.
- Health alliance for prudent prescribing, yield and use of antimicrobial drugs in the treatment of respiratory tract infections) is a project on respiratory tract infections in general practice. The objective of the project is to improve the quality of diagnostic procedures and treatment of respiratory tract infections in order to ensure that patients get only necessary antibiotics. The project expects to be able to reduce the total antibiotic prescribing rate to help avoid development of resistance. It developed intervention programmes targeting general practitioners (GPs), parents of young children and healthy adults, including guidelines, courses for GPs, workshops and patient information leaflets for improving the quality of antibiotic prescription.

US activities

- CDC is collaborating with the Infectious Diseases Society of America to update practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. In addition, CDC is working with an expert panel and the American Academy of Pediatrics to update the [Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Tract Infections](#).

Product labelling and literature

Joint activities

- The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) each have staff assigned to work in the other agency, allowing candid, rapid and confidential exchange of information regarding practices and policies that affect product labelling and other regulatory issues.

EU activities

- [Paediatric Regulation](#): New legislation governing the development and authorisation of medicines for use in children aged 0 –17 years was introduced in the European Union in January 2007. The new piece of legislation – Regulation (EC) No 1901/2006 as amended – introduces sweeping changes into the regulatory environment for paediatric medicines, designed to better protect the health of children in the EU. The Paediatric Regulation also brings in many new tasks and responsibilities for the European Medicines Agency (EMA), chief of which is the creation and operation of a Paediatric Committee within the Agency to provide objective scientific opinions on any development plan for medicines for use in children. Medicines are used in children despite a relative lack of information on how to prescribe safely. This is called off-label use. The

Paediatric Regulation aims to improve the information available to prescribers and families and therefore to reduce off-label use.

US activities

- FDA has had [labelling regulations addressing the proper use of antibiotics](#) since 2003 (21 CFR Part 201). Antibiotic drug labelling contains required statements at the beginning, in the "Indications and Usage" section, and in the "General" subsection of the "Precautions" section advising healthcare professionals that these drugs should be used only to treat infections that are believed to be caused by bacteria. In the "Information for Patients" subsection of the "Precautions" section, labelling also encourages healthcare professionals to counsel patients about proper use.

B. Surveillance of consumption of antibacterial agents in medical communities

EU activities

- [ESAC](#) (European surveillance of antimicrobial consumption) is a European project coordinated by the University of Antwerp, Antwerp, Belgium. There are 34 countries participating in ESAC including all 27 European Union Member States. Each country has its own national network of experts. Data on the use of drugs to treat infections caused by bacteria (antibiotics), viruses (antivirals) and fungi (antimycotics) are collected in a standard manner across countries.
- [ARPEC](#) (Antibiotic resistance and prescribing in European children) is a network that will develop a prospective surveillance system to monitor rates of antibiotic prescribing and resistance in EU children. This surveillance will be used to determine the variation in choice of drug, dose and indications for community and hospital antibiotic prescribing for common childhood infections between EU countries. ARPEC will propose a novel paediatric defined daily dose (DDD) methodology for comparison of hospital-based antibiotic prescribing for children (current DDD guidelines are based on adult dosage). Other activities will include a prevalence survey to compare antibiotic use in children in hospital, setting early benchmarks for prescribing and resistance rates and working with clinical experts of the European Society for Paediatric Infectious Diseases (ESPID) to implement the benchmarks and encourage the development of prudent and more unified EU-wide treatment guidelines.
- [APRES](#) (Appropriateness of prescribing antibiotics in primary healthcare in Europe with respect to antibiotic resistance) is a project that investigates the appropriateness of prescribing antibiotics in primary healthcare. In nine European countries data are being collected on antibiotic resistance patterns of bacteria circulating in the community. This will be compared with antibiotic prescribing patterns retrieved from primary care practices in an analysis to determine the relationship between the antibiotic resistance pattern for bacteria and the pattern of antibiotic prescription behaviour.
- [Self-medication with antimicrobial drugs in Europe](#) (SAR) is a project that recruited European countries from two networks of surveillance systems: ESAC and EARSS. The project's goal was to compare the prevalence of antimicrobial drug self-medication in the previous 12 months and intended self-medication and storage and to identify the associated demographic characteristics.
- ECDC developed a methodology for conducting point prevalence surveys on healthcare-associated infections (HAI) and antimicrobial use in acute care hospitals, to respond to the Council Recommendation of 9 June 2009 on patient safety, including prevention and control of HAI and provide support to the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine. Pilot point prevalence surveys sponsored by ECDC and supported by the University of Antwerp, Belgium, were performed to test this methodology. Experts from EU Member States gathered at the EU Conference organised jointly by the Belgian EU Presidency and ECDC in Brussels on 8–10 November 2010 concluded that, in view on these successful pilot surveys, all EU Member States should conduct the first EU point prevalence survey based on this methodology by November 2012 and repeat the survey at least once every five years.
- [HALT](#) (Healthcare-associated infections in long-term care facilities) is a project funded by ECDC to extend the control of healthcare-associated infections and antimicrobial resistance in European long-term care facilities by implementing a EU-wide (27 EU Member States, 3 EEA/EFTA and 3 EU candidate countries) network of networks in long-term care facilities and by performing repeated point prevalence surveys on healthcare-associated infections, antimicrobial resistance, antibiotic use, current infection control and antimicrobial stewardship practices and resources.

US activities

- The National Healthcare Safety Network (NHSN) is a voluntary, secure, internet-based surveillance system that integrates patient and healthcare personnel safety surveillance systems managed by the Division of Healthcare Quality Promotion (DHQP) at CDC. Enrolment in NHSN is open to all types of healthcare facilities in the United States, including acute care hospitals, long-term acute care hospitals, psychiatric hospitals, rehabilitation

hospitals, outpatient dialysis centres, ambulatory surgery centres, and long-term care facilities. CDC is launching a new version of the Antibiotic Use Module of the NHSN that will permit electronic reporting of antimicrobial use data from healthcare facilities. This module will be pilot tested in early 2011, with plans for a full launch later in 2011.

- CDC's [National Ambulatory Medical Care Survey \(NAMCS\)](#) provides data on antibiotic prescribing by condition. NAMCS is a national survey designed to collect objective, reliable information about the provision and use of ambulatory medical care services in the United States. Findings are based on a sample of visits to non-federal employed office-based physicians who are primarily engaged in direct patient care. In addition, CDC currently is in the process of gaining access to proprietary antibacterial consumption data that may allow for comparisons in antimicrobial consumption rates and trends between countries.
- CDC and the 10-state Emerging Infections Program (EIP) will launch a healthcare-associated infection and antimicrobial use point prevalence survey in 2011 to be conducted in general, acute-care hospitals in the 10 EIP states. The 2011 survey will yield information on the burden and types of healthcare-associated infections affecting patients hospital-wide, as well as the frequency and types of antimicrobial drugs being administered to patients and the rationale for their use.

C. Promotion of training of health professionals in medical communities

US activities

- CDC is supporting the development of web-based medical school curriculum on appropriate antibiotic use based on curriculum that has been pilot tested at several medical schools. This curriculum was originally developed in 1999 under contract with WESTAT (a research organisation) and the University of California, San Diego, for the development of a curriculum to teach medical students about the appropriate use of antibiotics in hospital and outpatient settings. This curriculum will be part of a larger curriculum for fourth-year medical students that will teach concepts from basic science in the context of clinical care.
- CDC's Get Smart: Know When Antibiotics Work programme is developing a continuing education programme and new web content that will train community pharmacists in appropriate antibiotic use education. Educational materials and guidelines for healthcare providers are already available online. Additional guidelines are in development.
- The Get Smart for Healthcare program is planning a number of training/educational opportunities for healthcare professionals, including: a CME programme at the annual IDSA meeting on antimicrobial stewardship (co-sponsored by SHEA/IDSA) and an online CME programme on antimicrobial stewardship for community hospitals. The Get Smart for Healthcare Website will also feature a variety of training and educational materials.

D. Information/education campaigns in medical communities

EU activities

- Full issue of [Eurosurveillance](#) dedicated to the topic of antimicrobial resistance was published in coordination with European Antibiotic Awareness Day 2010 with articles from ECDC, France, the Netherlands and multinational groups.
- ECDC is funding the development of a pilot [e-learning module](#) for continuous medical education on use of antibiotics in hospitals by the Dutch Working Party on Antibiotic Policy (*Stichting Werkgroep Antibiotica Beleid – SWAB*). This module consists of a series of questions and provides immediate feedback to answers with the objectives of improving knowledge, attitudes and behaviour on principles of prudent antibiotic use, including antibiotic stewardship strategies. In the future, the module will be used to evaluate the impact of information/education campaigns on prudent antibiotic use on hospital prescribers.
- [e-Bug](#) is a European-wide antibiotic and hygiene teaching resource for junior and senior school children. This resource not only reinforces an awareness of the benefits of antibiotics, but also teaches prudent antibiotic use and how inappropriate use can have an adverse effect on an individual's good microbes and antibiotic resistance in the community. The project is led by the Health Protection Agency (HPA) Primary Care Unit in Gloucester, UK, and involves a consortium of 18 partner EU countries. Project development was 60% funded by DG SANCO. From 2010 the website will be supported by the Health Protection Agency in England. The European Centre for Disease Prevention and Control (ECDC) supported translation of all the resources into the other EU-27 European languages through 2010, in time for the European Antibiotic Awareness Day.
- ECDC developed a toolkit of template materials for national health authorities to adapt and use as part of national campaigns on appropriate antibiotic use for hospital prescribers. Endeavours to assist intervention planners to understand, shape and develop effective communication strategies and tactics come under the rubric of formative evaluation. Formative evaluation of the toolkit has been undertaken through research with stakeholder groups

with the aim of developing consensus on toolkit components. This formative evaluation had two stages: a questionnaire survey followed by a consensus building exercise. A [report](#) on the consensus building exercise is available.

➤ Ongoing activities addressing appropriate therapeutic use of antibacterial drugs in veterinary communities

A. Measures to support appropriate therapeutic use (of antibacterial agents) in veterinary communities

Antibacterial stewardship programmes

Joint activities

- WHO Advisory Group on Integrated Surveillance on Antimicrobial Resistance (AGISAR).
- Other international activities where the US and the EU have participated:
 - [Codex Alimentarius](#) ad hoc Intergovernmental Taskforce on AMR;
 - [OIE Terrestrial Animal Health Code](#) and [Aquatic Animal Health Code](#);
 - Reports of the [FAO/WHO/OIE Expert meetings](#) on critically important antimicrobials;
 - [Codex Code of Practice to Minimize and Contain Antimicrobial Resistance](#).

EU activities

- The EU has adopted, for example, following [legal provisions](#):
 - Marketing authorisation requirements, antimicrobials prescription-only medicines (Veterinary Medicines Directive 2001/82/EC);
 - Monitoring and reporting of antimicrobial resistance in Salmonella, Campylobacter and indicators, MRSA survey in pigs (Zoonoses Monitoring Directive 2003/99/EC, Commission Decision 2007/407/EC, Commission Decision 2008/55/EC);
 - Ban to use antimicrobials in Salmonella eradication in poultry (Commission Regulation 1177/2006).
- [Council of the European Union](#) has adopted several conclusions related to antimicrobial resistance and use of antimicrobials in veterinary medicine (doc 13920/99, doc 9637/08 and doc 14867/10).
- The European Commission has taken, for example, the following initiatives to tackle AMR:
 - A staff working paper of the services of the Commission on AMR 2009 ([SANCO/6876/2009r6](#));
 - An upcoming Communication on a 5-year strategy on AMR.
- Research related to animal health, biosecurity on farms, vaccines, bacteriophages, breeding of more robust or disease resistant animals, substitutes to antimicrobial growth promoters.
- The [EPRUMA](#) (European Platform on Prudent Use of Antimicrobials in animals) is a joint initiative within the EU to bring together industry, manufacturers, animal owners, vets and pharmacists to promote the prudent use.
- As an example, the following activities have been undertaken by different EU Member States:
 - Animal healthcare programmes/agreement systems. They aim to improve vet-farmer cooperation, animal health and welfare and prudent use of medicines;
 - Recommendations and prudent use guidelines on antimicrobial use on species/indication/dosage level, recommendations on preventing MRSA infections in animals;
 - Restrictions on off-label use, ban of the use of human last resort antimicrobials;
 - Specific requirements for pre-treatment susceptibility testing, for group treatments;
 - Strategic programmes involving human and veterinary medicine, joint AMR surveillance;
 - A special attention to 3rd and 4th generation cephalosporins, fluoroquinolones and macrolides; at national level special requirements or restrictions;
 - Enforcement measures (veterinarians and farmers).
- The EMA has published recommendations on use and authorisation of [quinolones](#), [3rd and 4th generation cephalosporins](#) and [macrolides](#).

US activities

- The FDA and the American Veterinary Medical Association (AVMA) developed outreach materials on judicious use targeted to food animal producers. These consist of a series of booklets that explain antimicrobial prudent use principles in depth for beef cattle, dairy cattle, swine, poultry and aquatic veterinarians. See <http://www.avma.org/issues/default.asp> then continue down page to find each species.

- FDA awarded a contract to develop a web-based decision support system for use by veterinarians to select and use antimicrobial agents appropriately, the Veterinary Antimicrobial Decision Support ([VADS](#)) System that continues to be revised and improved.
- The US Interagency Task Force on Antimicrobial Resistance and [Public Health Action Plan to Combat Antimicrobial Resistance](#) was created in 1999 to develop a national plan to combat antimicrobial resistance. It is co-chaired by FDA, CDC and the National Institutes of Health/National Institute for Allergy and Infectious Diseases (NIH/NIAID). Agencies report annually on progress. The taskforce also includes the Agency for Healthcare Research and Quality, Centers for Medicare and Medicaid Services, Health Resources and Services Administration, United States Department of Agriculture (USDA), Department of Defense, Department of Veterans Affairs and the Environmental Protection Agency. In 2001, the US Agency for International Development joined the taskforce to help address global antimicrobial resistance issues.
- The National Antimicrobial Resistance Monitoring System ([NARMS](#)), established in 1996, continually monitors antimicrobial resistance among enteric bacteria (e.g. Salmonella, Campylobacter, *E. coli*, Enterococcus) in animals presenting for slaughter, animals on farm, humans, and retail meat. Animals include cattle, swine, chickens and turkeys; retail meat includes beef, pork and poultry.

Appropriate use of diagnostic tests

Joint activities

- Both the EU and the US participate in the Codex Taskforce on Antimicrobial Resistance, which promotes the use of and improving availability, speed, and accuracy of diagnostic microbiological tests.

EU activities

- [EU reference laboratory](#) and national reference laboratories in each Member State (MS) for antimicrobial resistance were established 2006. The EU-RL aims to develop and distribute methods for resistance analyses and to provide training and assistance to national reference laboratories.
- In some EU MS, certain antimicrobials (e.g. fluoroquinolones) cannot be used unless a recent diagnostic test reveals that no other antimicrobial is effective for that disease in that specific herd. Appropriate diagnostic testing is controlled and compared to the treatment guidelines. In some MS, microbiological diagnosis is required before group medications can take place.

US activities

- Antimicrobial resistance testing method development and training is done in conjunction with NARMS.
- FDA and CDC participate in the Clinical Laboratory Standards Institute (CLSI), Veterinary Subcommittee.

Product labelling and literature

Joint activities

- Both the EU and the US participate in the Codex Taskforce on Antimicrobial Resistance, which has addressed product labelling and literature as an important aspect on controlling antimicrobial resistance.

EU activities

- [European Medicines Agency's](#) Committee for Veterinary Medicinal Products (CVMP) has guidelines on the Summary of Product Characteristics (SPC) for antimicrobial products.
- CVMP has developed a [reflection paper](#) on the use of fluoroquinolones and 3rd and 4th generation cephalosporins in food producing animals. These papers contain recommendations for precautions regarding prudent use to be included in the SPCs for such products. The CVMP has been using referrals as a legal tool to implement prudent use warnings on the SPC of some antimicrobials (e.g. (fluoro) quinolones).

US activities

- FDA [Guidance for Industry #152](#), Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern, provides a non-binding pre-approval mechanism to evaluate the safety of antimicrobial animal drugs with regard to their microbiological effects on bacteria of human health concern. The guidance lays out a qualitative risk assessment approach to antimicrobial animal drugs intended for use in food-producing animals, as well as potential risk management strategies to minimise impact on human health.

- FDA has produced several quantitative risk assessments on the issue of antimicrobial resistant bacteria in animals, due to the use of antimicrobial drugs in animals, transferring to humans and causing antimicrobial-resistant infections, e.g., fluoroquinolone-resistant *Campylobacter* in poultry, macrolide resistance, others. For qualitative risk assessments, see Guidance for Industry #152, above.
- FDA draft [Guidance for Industry #209](#), The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals, published 28 June 2010, summarises some of the key scientific reports on the use of antimicrobial drugs in animal agriculture. It outlines FDA’s current thinking on strategies for assuring that medically important antimicrobial drugs are used judiciously in food-producing animals in order to help minimise antimicrobial resistance development.

Addressing inappropriate off-label use

EU activities

- In the EU no maximum residue limits for cephalosporins are established for poultry, as a result cephalosporins cannot be used systematically in poultry apart from “off-label or extra label”. This use does not cover continuous *in ovo* injection or treatment of 1-day-old chicks. The European Medicines Agency is trying to reinforce the message that cephalosporins should not be used in poultry. The Agency is exploring the legal possibility to include in all SPCs for cephalosporins a specific prohibition of off-label use, such as the phrase “Do not use in poultry”.
- Regarding antimicrobial resistance linked to the use of antimicrobial agents in companion animals, the CVMP has started considering the use of certain antimicrobials and the risk for antimicrobial resistance. Some of those considerations are reflected on a recently published document on MRSP (methicillin-resistant *Staphylococcus pseudintermedius*)
- In some EU MS there are restrictions/ban on off-label use and restrictions to use certain human critically important antimicrobials in all animal species.

US activities

- The FDA [prohibits the extra-label use](#) of certain antimicrobials in food-producing animals due to the threat of public health harm, including fluoroquinolones and glycopeptides.
- The FDA rescinded the approval of [fluoroquinolones for use in poultry](#), effective September 2005. Also see 1c.2. for additional regulatory actions.

Over-the-counter sales

EU activities

- In the EU, all veterinary antimicrobials are prescription-only medicines.

US activities

- FDA issued the 2010 draft [Guidance to Industry #209](#) requesting comment on plans to limit medically important antimicrobial drugs in food-producing animals to those uses that have veterinary oversight or consultation. This would be prescription status or status similar to prescription for in-feed use (Veterinary Feed Directive).

B. Surveillance of consumption of antibacterial agents in veterinary communities

EU activities

- The European Surveillance of Veterinary Antimicrobial Consumption ([ESVAC](#)) project, coordinated by the European Medicines Agency, started in 2009. It aims to collect data generated from surveillance of the sales of antimicrobial agents for use in animals to identify and quantify risk factors for the potential development and spread of antimicrobial resistance in animals.

US activities

- FDA is implementing Section 105 of the Animal Drug User Fee Amendments of 2008 to collect animal [antimicrobial drug distribution data and make summaries of such data publically available](#).

C. Promotion of training of health professionals in veterinary communities

EU activities

- Some EU Member States have animal healthcare programmes including extensive training of veterinarians and farmers and audits. Audits can be seen as training for veterinarians.
- Some EU MS have established national cooperation bodies involving veterinary practitioners from different areas, as well as human health experts and competent authorities.
- Some MS organise education of veterinarians, farmers and other owners of animals.

US activities

- FDA awarded a contract to develop a web-based decision support system for use by veterinarians to select and use antimicrobial agents appropriately, the Veterinary Antimicrobial Decision Support ([VADS](#)) System that continues to be revised and improved.
- FDA produced a nine-minute [animation](#) explaining to veterinarians how antimicrobial resistance both emerges and proliferates among bacteria.
- FDA produced several [videos](#) and accompanying booklets on antimicrobial prudent use.
- Through the Get Smart on the Farm programme, CDC awarded funds to Michigan State University to develop an interactive web-based educational programme aimed at teaching and promoting the prudent use of antimicrobial agents in veterinary medicine, [The Antimicrobial Resistance Learning Site for Veterinary Students](#).

D. Information/education campaigns in veterinary communities

EU activities

- [European Antibiotics Awareness Day](#) is used by many EU Member States as an opportunity to organise information campaigns on AMR and prudent use of antimicrobials at national level also for veterinary medicine.
- [EPRUMA](#) is a multi-stakeholder platform linking best practice with animal health and public health. It aims to promote the responsible use of medicines in animals in the EU.

US activities

- The FDA and the American Veterinary Medical Association (AVMA) developed outreach materials on judicious use targeted to food animal producers. These consist of a series of booklets that explain antimicrobial prudent use principles in depth for beef cattle, dairy cattle, swine, poultry and aquatic veterinarians. See <http://www.avma.org/issues/default.asp> then continue down page to find each species.

2. Prevention of drug-resistant infections

A. Ongoing activities – Surveillance

Joint activities

- National point prevalence survey of antimicrobial use and healthcare-associated infections (HAI). Since 2009, CDC staff have visited ECDC and worked with EU investigators in attempts to harmonise key methods related to ECDC EU prevalence survey and US efforts. Both efforts are on time for a 2011 implementation, and results would allow for some comparisons between US and EU.

EU activities

- The European Antimicrobial Resistance Surveillance Network ([EARS-Net](#)), previously known as the European Antimicrobial Resistance Surveillance System (EARSS), is a European-wide network of national surveillance systems providing European reference data on antimicrobial resistance for public health. It is coordinated by ECDC.
- The Healthcare-Associated Infections Network ([HAI-Net](#)) is the European network for the surveillance of HAIs. It is coordinated by ECDC and is largely based on the experience and activities of former networks financed by DG

SANCO of the European Commission, namely HELICS (Hospitals in Europe Link for Infection Control through Surveillance) and IPSE (Improving Patient Safety in Europe).

- [DebugIT](#) (Detecting and Eliminating Bacteria Using Information Technology) is a project financed by the Directorate-General Information Society (DG INSO) of the European Commission. It will use clinical and operational information from clinical information systems (CIS) across the European Union and data mining techniques to monitor and provide decision support to prevent harmful patient safety events, including AMR. The benefits of this approach in terms of clinical and socio-economic outcomes will be measured.
- [TROCAR](#) (Translational Research On Combating Antimicrobial Resistance) is a project that focuses on defining the major high-risk resistant clones, exploring genomic and proteomic approaches to investigate specific traits of epidemic clones, and developing bioinformatics tools to exploit genomics data. By combining the outputs of the project, TROCAR aims at providing the scientific basis for an early warning system when isolates of a particular epidemicity appear in the community and in hospitals.

US activities

- [Active Bacterial Core Surveillance](#): Active laboratory- and population-based surveillance system for invasive bacterial pathogens of public health importance, including *Haemophilus influenzae*, *Neisseria meningitidis*, group A Streptococcus, group B Streptococcus, *Streptococcus pneumoniae* and MRSA. ABCs also provides an infrastructure for further public health research, including special studies aiming at identifying risk factors for disease, post-licensure evaluation of vaccine efficacy and monitoring effectiveness of prevention policies. ABCs reaches about 42 million people and operates in 10 Emerging Infections Program (EIP) sites around the United States.
- Healthcare Associated Infections-Community Interface ([HAIC](#)) projects: Active population-based surveillance for *Clostridium difficile* infection and other healthcare-associated infections caused by pathogens such as *Candida* and multidrug resistant Gram-negative bacteria. Sites also utilise the National Healthcare Safety Network (NHSN) to perform time-limited evaluations of HAIC data among NHSN facilities participating in the EIP NHSN network.
- [Surveillance for healthcare-associated infections using NHSN](#): For a description of NHSN, see I.1.b.7. CDC measures healthcare-associated infections and antimicrobial resistance associated with these infections in NHSN. In aggregate, CDC analyses and publishes surveillance data to estimate and characterise the national burden of healthcare-associated infections. At the local level, the data analysis features of NHSN that are available to participating facilities range from rate tables and graphs to statistical analysis that compares the healthcare facility's rates with the national aggregate metrics.

B. Ongoing Activities – Prevention

EU activities

- The project "[ABS INTERNATIONAL](#): Implementing antibiotic strategies for appropriate use of antibiotics in hospitals in Member States of the European Union" (2006–2008, involved nine EU Member States) developed training and guidance documents on strategies, organisation and structure and process indicators for hospital antimicrobial stewardship programs. (Allerberger F, Expert Rev Anti Infect Ther 2009; 7:1175-83).
- ECDC systematic review and evidence-based guidance on peri-operative antimicrobial prophylaxis and organisation of hospital infection control programmes (subcontracted to external experts) will be developed over 2010–2012 to include evidence-based guidance, structure and process indicators as well as implementation of toolkits where appropriate.
- [IMPLEMENT](#) (Implementing strategic bundles for infection prevention and management) is a project that aims to identify current national and local implementation strategies for the prevention and management of central venous line infections and ventilator-associated pneumonia as well as for antimicrobial chemotherapy. IMPLEMENT will develop and test an optimal strategy for the implementation of bundles for infection prevention and management.
- [PROHIBIT](#) (Prevention of hospital infections by intervention and training) is a projects that aims to understand existing guidelines and practices to prevent HAIs in European hospitals, to identify factors that enable and reduce compliance with best practices, and to test the effectiveness of interventions of known efficacy. PROHIBIT will develop recommendations for the EU, policy makers, managers and medical professionals.
- [MOSAR](#) (Mastering hOSPital Antimicrobial Resistance and its spread into the community) is a network that integrates and coordinates multidisciplinary prevention and control activities of 16 hospitals in 9 European countries. In particular, MOSAR is conducting three interventional clinical trials to test the efficacy of measures to

prevent and control spread of MDR organisms in intensive care units, surgical units and rehabilitation centres, respectively.

US activities

- [Control of Carbapenem-Resistant Enterobacteriaceae \(CRE\)](#): Detection and prevention guidelines published in March, 2009. Recent importation of NDM-1 and other novel CRE mechanisms has led to refocusing public health response. Several states currently assessing local epidemiology and prevention practices being used by healthcare delivery sector.
- American Recovery and Reinvestment Act (ARRA): Funded state MRSA, *Clostridium difficile* and other MDRO prevention collaboratives using standardised strategies and assessment instruments. See toolkits [here](#).
- [CDC's Prevention Epicenters \(PE\) Program](#): CDC's Division of Healthcare Quality Promotion (DHQP) collaborates with academic investigators to address important scientific questions regarding the prevention of healthcare-associated infections (HAIs), antibiotic resistance, and other adverse events associated with healthcare. These Epicenters study such topics as MRSA, VRE and other multidrug-resistant bacterial pathogens; bloodstream infections; surgical site infections; ventilator-associated pneumonia; *C. difficile*; and catheter-associated urinary tract infections.
- The Healthcare Infection Control Practices Advisory Committee ([HICPAC](#)): Fourteen external infection control experts provide advice and guidance to the CDC and HHS regarding the practice of healthcare infection control, strategies for surveillance and prevention and control of healthcare-associated infections in US healthcare facilities. One of the primary functions of the committee is to issue recommendations for preventing and controlling healthcare-associated infections in the form of guidelines, resolutions, and informal communications.
- A statewide collaborative to prevent infections caused by multidrug-resistant organisms (MDROs): CDC is conducting a statewide collaborative in Vermont that involves nearly all the acute and long-term care facilities in the state. This effort targets clusters of acute and long-term care facilities from the same areas and attempts to implement regional strategies for MDRO prevention. In addition, the effort will utilise electronic data collection to measure outcomes. The goal of this effort will be to both decrease transmission of MDROs already present in Vermont and to prevent the emergence of new MDROs.
- A multi-state collaborative to assess the dynamics of MDRO contamination in the healthcare environment and the impact of environmental cleaning and disinfection methods. CDC is working with state health departments in Illinois, Vermont and Maryland to coordinate a prevention collaborative, which includes both acute care hospitals and nursing homes.

C. Ongoing Activities – Training

Joint activities

- The [ESCMID/SHEA Training Course in Hospital Epidemiology](#) was first established in 1999 and has been approved by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Society for Healthcare Epidemiology of America (SHEA). This intensive training programme aims at those working with infection control and hospital epidemiology. It covers epidemiology and infection control within the hospital setting. This course features international experts and offers basic, advanced and applied modules. It is run each year, and, over the years, it has evolved into the leading European course in its field, with over 1 000 alumni.

EU activities

- [TRICE](#) (Infection control training needs assessment in the European Union) is a project funded by ECDC that reviewed information on human resources and training in infection control in European countries. TRICE identified a need to standardize infection control training in Europe developed a core curriculum for this purpose.

US activities

- New tools to measure adherence to infection control recommendations in healthcare facilities: CDC is working with academic partners to develop an iPhone/iPod Touch application to assist observers (including patients) in evaluating adherence to recommended hand hygiene and isolation precaution practices. The application has been deployed in several CDC-led outbreak investigations and has been used by members of various prevention collaboratives for consistent and efficient data collection by observers.
- Preventing MRSA infections in VA medical centres: CDC is working with acute care VA medical centres nationwide in an effort to decrease MRSA healthcare-associated infections. MRSA HAI rates declined 24% in the non-ICU setting and 77% in the ICU setting, following full implementation of interventions. Analyses will include

monitoring changes in the *Staphylococcus aureus* antibiogram following implementation of the programme and an examination of factors that explain variability of impact among individual facilities.

D. Ongoing activities – Campaigns

Joint activities

- Participation in [WHO Patient Safety Campaigns](#), e.g. hand hygiene and tackling antimicrobial resistance.

US activities

- [National MRSA Education Initiative](#): A campaign to help Americans better recognise and prevent MRSA skin infections through public service announcements and educational materials for healthcare providers. The initiative provides information that can help prevent the spread of MRSA, recognise infection and treat those who are infected.

3. Strategies to improve the pipeline of new antibacterial drugs

A. Ongoing research activities

US activities (NIH/NIAID)

Basic research

- Investigator-initiated research grants comprise the bulk of NIH funding. A complete list of funded antimicrobial resistances grants can be found at the [NIH RePORT website](#). Examples of antimicrobial resistance topics covered in NIH/NIAID's grants portfolio are:
 - Mechanisms of resistance;
 - Antimicrobial, diagnostic and vaccine target identification and characterisation;
 - Discovery of new chemical entities with antimicrobial activity.

International investigators are eligible for most [investigator-initiated grant mechanisms](#).

- NIH/NIAID issues calls for applications (grants) and proposals (contracts) in specific targeted areas each year. A comprehensive and current list of these announcements can be found in the [NIH Guide for Grants and Contracts](#).
- NIH/NIAID has made a significant investment in genomic-related activities that provide genomic sequencing, functional genomics, bioinformatics and proteomic resources and reagents to the scientific community. For example, NIH/NIAID has sequenced more than 800 bacterial strains including more than 100 *S. aureus* strains that are in GenBank. In addition, Actinomycetes are being sequenced and mined for antibiotic gene cluster for potential new antibiotics. Protein expression clones and DNA microarrays are available for a large number of bacteria and 3D structures of many bacterial proteins have been completed or are in process of being done. NIH/NIAID supports Bioinformatics Resource Centers that serve as collect, integrate and provide open access to research data of microbial organisms in a user friendly format for the scientific community, including bioinformatics analysis capability and tools. These services are available to the international research community. More information can be found [here](#).

Translational research

- NIH/NIAID provides a broad array of preclinical and clinical research resources and services to researchers in academia and industry designed to facilitate the movement of products from bench to bedside. By providing these critical services to the research community, NIH/NIAID can help to bridge gaps in the product development pipeline and lower the financial risks incurred by industry to develop novel antimicrobials. These services are available to the international research community with appropriate preliminary data. More information can be found [here](#).
- NIH/NIAID's Partnerships Program supports collaborative efforts and multidisciplinary approaches between academia and the pharmaceutical industry to advance candidate products or platform technologies through the product development pathway, and has supported numerous grants addressing resistance since its inception in 2000. For example, in FY10, NIH/NIAID awarded 19 milestone-driven grants under the "Partnerships for the Development of Therapeutics and Diagnostics for Drug-Resistant Bacteria and Eukaryotic Parasites" research initiative ([RFA AI-09-026](#)). The partnership programme also featured initiatives to stimulate the development of new diagnostic technologies for resistant pathogens in [2004](#), [2006](#) and [2008](#). International institutions are eligible for partnership grants.

Clinical research

- NIH/NIAID supports clinical trials infrastructure focused primarily on evaluating new drugs through the Vaccine and Treatment Evaluation Units (VTEUs) and the Phase I Clinical Trial Units for Therapeutics, as well as through investigator-initiated clinical trials. Use of the Phase I clinical trial units is available to the international research community. More information can be found [here](#).
- NIH/NIAID is also supporting clinical trials to inform the rational use of existing antimicrobial drugs to help limit the development of antimicrobial resistance. Since 2007, NIH/NIAID has made 8 awards for targeted clinical trials designed to help answer key questions about proper antimicrobial dose, treatment duration and whether antimicrobial treatment is necessary in all cases. All of these trials are ongoing or in development. More information about each trial can be found at the following links: skin and soft tissue infections caused by CA-MRSA ([2007](#)); catheter-related bacteremia and urinary tract infections ([2009](#)); Gram-negative bacteremia, acute otitis media and community-acquired pneumonia ([2010](#)).

EU activities (European Commission/Directorate-General for Research and Innovation (DG RTD))

- The European Commission issues annual calls for proposals under the Seventh Framework Programme for Research and Technological Development (FP7, 2007 - 2013). Research and innovation on AMR has a high priority and support is provided in different parts of FP7: 1) Under the Ideas programme (managed by the European Research Council, which was set up in 2007 to support investigator-driven frontier research; 2) through the Cooperation programme of FP7 (manged by the Directorate-General for Research & Innovation) notably under the "Health" theme, which accounts for the major part of the AMR funding, but also through the theme "Food, agriculture and fisheries, and biotechnology", and to a lesser extent under the theme "Information and Communication Technologies".

Collaborative research projects funded under FP7 must have partners from at least three EU Member States (or associated countries), but may include non-EU partners. Research projects funded within the Health theme are open for US participation and US partners are eligible for funding (EU–NIH agreement on funding reciprocity). More information on international cooperation can be found [here](#).

In general, research supported via FP7 addresses one of the following broad areas:

- Developing strategies for prudent/rational use of currently available drugs – Research projects in this area aim at slowing down the rise in the development of resistance and reduce the spread of resistant microbes.
- Basic research on pathogens and host pathogen interactions.
- Defining optimal treatment regimens of antimicrobials - Research projects in this area include investigator-driven clinical trials of off-patent antibiotics.
- Developing novel antimicrobial therapies – Research projects in this area focus on new use of existing antibiotics, the development of new antibiotics or the identification of new drug targets.
- Developing new rapid cost-effective diagnostic tests – The development of diagnostic tests is required to aid diagnosis and to determine whether antibiotics should be prescribed, and which antibiotics should be prescribed.
- Validation of diagnostic tests – The validation of diagnostic tests is required to determine performance, robustness, sensitivity, reliability, etc. in the clinical setting.
- Development of tools to control microbial biofilms with relevance to drug resistance – Disruption of biofilms or preventing their formation will improve treatment of infections.

The role of environmental reservoirs, veterinary medicine and animal husbandry in the spread of resistance to humans is also being addressed. AMR will be taken into account in the final years of FP7 and when developing the strategy for the next EU research Framework Programme, Horizon 2020.

More information on research projects that are funded under both the Sixth (2003-2006) and Seventh Framework Programmes can be found [here](#).

- The development of new antimicrobials is also boosted by collaborations with industry. This is shown by the contribution of small-medium-sized enterprises (SMEs) participating in FP7 research projects, but also through public-private-partnerships. An example of such an approach is the Innovative Medicines Initiative (IMI), Europe's largest public-private initiative that aims to speed up the development of better and safer medicines for patients. IMI is a joint undertaking between the European Commission and the European federation of pharmaceutical industry and associations (EFPIA). IMI supports collaborative research projects and builds networks of industrial and academic experts in Europe that will boost innovation. IMI currently funds a project called RAPP-ID, which aims to develop a point-of-care test for rapid detection of bacteria, fungi, viruses and markers of infection as well as resistance to the most commonly used antibiotics. Other topics in the area of AMR are under consideration for future IMI calls. More information can be found [here](#).

- The EU Member States have recognized the need to step up their collaboration to respond more efficiently to the challenges in the area of AMR. They have therefore agreed to set up a Joint Programming Initiative (JPI) aimed at better coordinating the Member States' own national research activities on AMR. The JPI "The Microbial Challenge – An Emerging Threat to Human Health" aims at providing a better scientific basis for a coordinated policy response to the emerging and increasing problem of AMR. This JPI is under development and is expected to become operational in 2012.

B. Ongoing regulatory activities

Joint activities

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Through the ICH, the EMA and the US FDA (in conjunction with other regulatory and industry stakeholders) have participated in the development of a number of guidance documents in the area of preclinical and clinical development of drugs. The available guidances¹⁷ include the following:
 - E8 General Considerations for Clinical Trials¹⁸
 - E9 Statistical Principles for Clinical Trials¹⁹
 - E10 Choice of Control Group and Related Issues in Clinical Trials²⁰
 - E11 Clinical Investigation of Medicinal Products in the Pediatric Population²¹
 - E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs²²
 - ICH M3(R2), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals²³

Of note is that the guidances listed above were developed by the ICH process – the result of which are guidances that are adopted by both the EMA and the US FDA. In addition to these, there are also guidance documents on a wide range of other topics in the area of drug development that serve as a valuable resource to persons who are interested in information on drug development. These resources include advice on manufacturing issues and a wide range of other topics.

US activities (FDA)

Recent and current activities in the area of antibacterial drug development

- The FDA has been working to update its guidance documents to describe recommended clinical trial designs for studying antibacterial drugs. In some circumstances, the FDA has held public workshops for the purposes of discussing the science or FDA Advisory Committee meetings to get advice on the design of clinical trials for studying antibacterial drugs for selected conditions. The workshops and Advisory Committee meetings held to date are listed below:
 - IDSA/FDA co-sponsored Community-Acquired Pneumonia (CAP) workshop; January 2008
 - IDSA/ATS/ACCP/SCCM/FDA co-sponsored Hospital Acquired Pneumonia/Ventilator Associated Pneumonia workshop; March/April 2009
 - IDSA/FDA/NIAID co-sponsored workshop on antimicrobial resistance; July 2010
 - FDA workshop – Issues in the Design and Conduct of Clinical Trials for Antibacterial Drug Development; August 2010
 - FDA workshop – Design of Clinical Trials of Aerosolized Antimicrobials for the Treatment of Cystic Fibrosis; September 2010
 - FDA Advisory Committee Meetings Focusing on clinical trial designs
 - Community Acquired Pneumonia April 2008; December 2009;
 - Acute Bacterial Skin and Skin Structure Infections; November 2008
- There have also been FDA Advisory Committee discussions on clinical trial design in the context of specific antibacterial drug products that informed the development of recommendations on clinical trial designs. These

¹⁷ Guidance Documents can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

¹⁸ The Guidance Document *E8 General Considerations for Clinical Trials* is available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073132.pdf>

¹⁹ The Guidance Document *E9 Statistical Principles for Clinical Trials* is available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf>

²⁰ The Guidance Document *E10 Choice of Control Group and Related Issues in Clinical Trials* is available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073139.pdf>

²¹ The Guidance Document, *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* is available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073143.pdf>

²² The Guidance Document, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*, is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf>

²³ The Guidance Document, *ICH M3(R2), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073246.pdf>

efforts to date have resulted in the publication of updated guidance documents in the area of antibacterial drug development or non-inferiority clinical trial designs. The guidance documents published to date include the following:

- Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval – Draft October 2007; Final November 2010
 - Acute Bacterial Sinusitis: Developing Drugs for Treatment – Draft October 2007
 - Acute Bacterial Otitis Media: Developing Drugs for Treatment – Draft January 2008
 - Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment – Draft August 2008
 - Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment – Draft March 2009
 - Noninferiority Clinical Trials – Draft March 2010
 - Acute Bacterial Skin and Skin Structure Infections – Draft August 2010
 - Hospital Acquired Bacterial Pneumonia / Ventilator Associated Bacterial Pneumonia – Draft November 2010
- In addition to the updated guidances listed above, there are several guidance documents that are being developed, updated or that are planned for development. The topic areas include the following:
- Update Draft Guidance on Community-Acquired Bacterial Pneumonia (CABP)
 - Urinary Tract infections, cUTI, and uUTI
 - Complicated Intra-Abdominal Infections (cIAI)
 - Serious Bacterial Infections with Unmet Need (e.g. bacterial infections where the infecting bacteria are resistant to multiple antibacterial drugs and few or no treatment options exist)
- The FDA also recently published a guidance on noninferiority trials that provides information on the conceptual approach to noninferiority trials, recommendations on design of such trials, interpretation and developing a noninferiority margin. In addition, for sponsors seeking guidance on trial designs for studying an antibacterial drug, the FDA division responsible for review of the product is available to meet with companies during product development to provide feedback and advice on their proposed development programme.

Regulatory tools for drug development

- FDA’s Center for Drug Evaluation and Research’s Pre-IND Program: Sponsors interested in developing a drug for treatment of a serious infection can contact the FDA and discuss their nonclinical and clinical development plans with the division responsible for the review of their product. CDER’s Pre-IND programme allows sponsors to receive direct feedback on their proposed submission of an IND, including the types of nonclinical studies that should accompany the IND. Sponsors have an opportunity to consider the recommendations they receive in planning their development programmes²⁴.
- Fast Track Designation: Companies that are developing a drug for the treatment of a serious disease that has the potential to address an unmet medical need can request fast track designation. The FDA developed fast track designation in order to facilitate development of such drugs²⁵. Under certain circumstances, even if there is existing therapy, a drug may still be granted fast track designation if there is evidence of advantages over existing therapy, such as improved efficacy or a better safety profile. The level of evidence to support fast track designation is commensurate with the stage of development. Sponsors with a drug that has received fast track designation are encouraged to meet frequently with the Agency to discuss clinical development plans. Sponsors may also submit completed sections of an NDA as part of a rolling review for the FDA to begin its evaluation prior to submission of the full marketing application.
- Priority Review Designation: Under the Prescription Drug User Fee Act (PDUFA), a goal for a specific time frame to complete the review of an NDA is established. For a product that receives a standard review, the PDUFA goal for completing the review is 10 months. For drugs that offer a major advance in treatment, or provide treatment where no therapy exists, the product may receive a priority review designation²⁶. The goal for completing a priority review of an NDA is six months.

EU activities (EMA)

Recent and current activities in the area of antibacterial drug development

²⁴ The Office of Antimicrobial maintains a Pre-IND Consultation website, which can be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm>

²⁵ Guidance for Industry: Fast Track Drug Development Programs — Designation, Development and Application Review. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079736.pdf>

²⁶ Manual of Policies and Procedures, Center for Drug Evaluation and Research, MAPP 6020.3 Review Classification Policy: Priority (P) and Standard (S), available at: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM082000.pdf>

- The core guidance document for the clinical development of antibacterial agents (CPMP/EWP/558/95 Rev2) was revised during 2009 - 2011. Before finalisation, a symposium was held in 1Q2011 at which regulators, industry and academia met to discuss the areas perceived to have particular implications for future development programmes. The draft revision carries a section specific to the development of new agents with potential to be clinically useful against multidrug-resistant bacteria and this will be one of the areas discussed at the symposium.
- The European Medicines Agency (EMA) does not currently produce indication-specific guidance (the exception being the addendum specific to tuberculosis). However, it has been agreed that an addendum will be produced to cover the most critical expectations for commonly sought indications. This is currently under development and should be released for consultation during 2011.
- The EMA has recently revised its Working Party (WP) practices and has just established an Infectious Disease Working Party (IDWP) to oversee guideline development and to contribute as needed on any specific issue in the field of infectious diseases arising from Committees discussions or scientific advice. In addition to this WP made up of regulators from some of the National Agencies across the EU, there is an independent advisory group of experts in the field of infectious diseases that may be called upon to advise the CHMP and IDWP as considered necessary.
- The EMA has in place a number of additional guidelines of high relevance to the development of antibacterial agents. It should be noted that the guidance regarding non-inferiority margins is also currently under revision:
 - Guideline on the choice of non-inferiority margin (EMEA/CPMP/EWP/2158/99 Rev)
 - Points to consider on application with 1. Meta-analyses 2. One pivotal study (CPMP/EWP/2330/99).
 - Points to consider on the pharmacodynamic/pharmacokinetic relationship (CPMP/EWP/2655/99)
 - Guideline on clinical trials in small populations (CHMP/EWP/83561/2005)
 - Extrapolation of results from clinical studies conducted outside Europe to the EU population (CHMP/EWP/692702/08)
- During the last two years, the EMA has collaborated with the European Centre for Disease Control (ECDC) to consider and publish an analysis of the gap between antibacterial drug development and emerging clinical need in light of increasing rates and types of antibacterial resistance. This report was presented and discussed at a meeting held in Stockholm in September 2009, which provided much of the impetus from the EU side for the development of TATFAR.

Regulatory tools for drug development

- Scientific advice: Scientific advice and protocol assistance is provided by the EMA to pharmaceutical companies. It is designed to speed up the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients. Scientific advice (and protocol assistance – the special form of scientific advice available for the development of medicines for 'orphan' or rare diseases) can be requested either during the initial development of a medicinal product (i.e. before submission of a marketing-authorisation application) or later on, during the post-authorisation phase.
- The Scientific Advice Working Party (SAWP) is a standing Working Party of the Committee on Human Medicinal Products (CHMP) and is responsible for drafting scientific advice on any aspect of a drug development programme (including manufacture, non-clinical and clinical evaluations). Final advice, with or without the need for a discussion meeting with the sponsor, is issued after consideration by the CHMP and in a procedure that takes a maximum of 90 days. Protocol assistance is free of charge and scientific advice carries a reduced fee for small companies that meet certain criteria (Small Medium Size Enterprises – SMEs)²⁷.
- Accelerated assessment: Once a centralised application has been filed to EMA, the total clock-on days is limited to 210. On request from sponsors and at the discretion of the CHMP, the total review time may be shortened when the product in question is considered to have potential to treat a serious disease and/or fulfils an unmet medical need²⁸. In case of the granting of a request for an accelerated assessment procedure, the EMA shall ensure that the opinion of the CHMP is given within 150 days.
- Conditional marketing authorisation: In the case of certain categories of medicinal products, in order to meet unmet medical needs of patients and in the interests of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally the case and subject to specific obligations, i.e. granting 'conditional marketing authorisations'. The categories concerned should be medicinal products that aim at the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, or

²⁷ EMA Scientific Advice guidance available on EMA website at:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800229b9

²⁸ CHMP Guideline on the procedure for accelerated assessment pursuant to article 14 (9) of regulation (EC) No 726/2004 available at: www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004136

medicinal products to be used in emergency situations in response to public health threats recognised either by the World Health Organization or by the Community.

- Although the data upon which an opinion on a conditional marketing authorisation is based may be less complete, the risk-benefit balance should be positive. Furthermore, the benefits to public health of making the medicinal product concerned immediately available on the market should outweigh the risk inherent in the fact that additional data are still required. The holder should be required to complete or initiate certain studies with a view to confirming that the risk-benefit balance is positive and resolving any questions relating to the quality, safety and efficacy of the product²⁹.

²⁹ Guideline on the scientific application and the practical arrangements necessary to implement commission regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of regulation (EC) No 726/2004 available at: www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WCS00004908

Annex F – Public consultation summary

As the taskforce is solely composed of civil servants, the US and EU partners agreed to solicit input from the public, interested experts and other stakeholders in accordance with each partner's respective process for obtaining public comment, on the specific activities within the framework of the Declaration where EU–US collaboration could be most fruitful. This was achieved through the organisation of:

- an online public consultation at EU level organised by the Public Health Department of the European Commission;
- a stakeholder listening session and a public meeting in the US organised by the Office of Global Health Affairs, HHS.

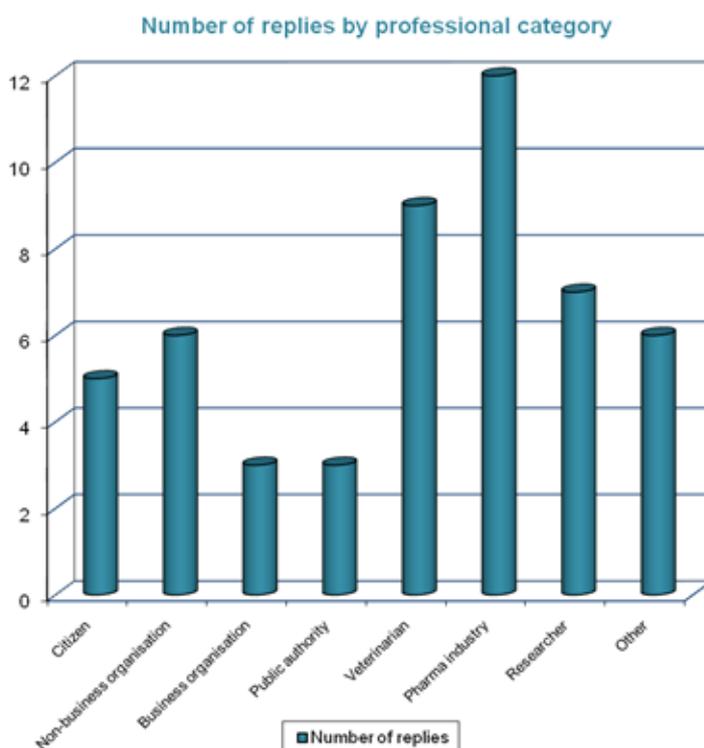
Online EU public consultation

The public consultation provided an opportunity for the public to submit their views on the Taskforce to the European Commission. The objective was to use this feedback for drafting the report to be submitted to the EU–US Summit of 2011. It could also provide input for other policy initiatives in relation to antimicrobial resistance.

The instrument used for the public consultation was a questionnaire. The online version of the questionnaire was prepared using the internet-based software package IPM (Interactive Policy Making). The consultation was open for contributions between 17 November and 17 December 2010. The questionnaire was composed of a mix of closed and open questions.

The launch of this consultation was announced on the websites of the Directorate-General for Health & Consumers (DG SANCO) and of the taskforce and through the Commission services, EU agencies and other national representatives involved in the taskforce. All contributions collected during this period were analysed and used to generate the conclusions put forward in this report. Comments submitted outside these dates or by means other than the online version of the questionnaire are also annexed to this report.

Forty-five respondents contributed to the online questionnaire providing electronic contributions. The majority of the responses were provided by two groups: representatives from the pharmaceutical industry (24%) and from the veterinarians (17%). Two additional written contributions were received separately from representatives of public authorities and non-business organisations.



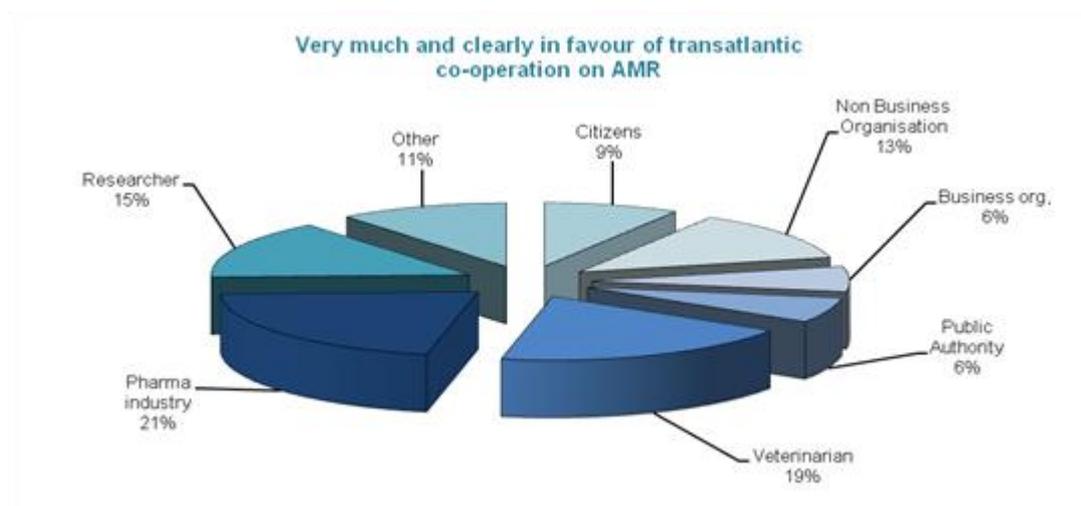
Based on the contributions received, the Commission published on 23 February 2011 a report reviewing and analysing the inputs received. This report identified the following key conclusions:

1. Broad support for transatlantic cooperation against AMR

A clear and net majority of the respondents have expressed a strong support in favour of such initiative.

| Are you in favour of transatlantic cooperation on AMR? | Number of requested records | % of total |
|--|-----------------------------|------------|
| Very much | 21 | 46.7% |
| Clearly | 20 | 44.4% |
| Somewhat | 2 | 4.4% |
| Not at all | 1 | 2.2% |
| Not much | 0 | 0% |
| Do not know | 0 | 0% |
| N/A | 1 | 2.2% |

A careful review of the breakdown of replies by category of respondents indicates that TATFAR support is across sectors.



2. TATFAR as a platform for the exchange of views, best practices and alignment of the initiatives and measures against AMR

The Commission asked stakeholders to indicate their expectations in terms of areas for and outcomes of the transatlantic cooperation on prudent use of therapeutic use in human and veterinary medicines, infection control and strategies to improve the pipeline of new antimicrobial drugs.

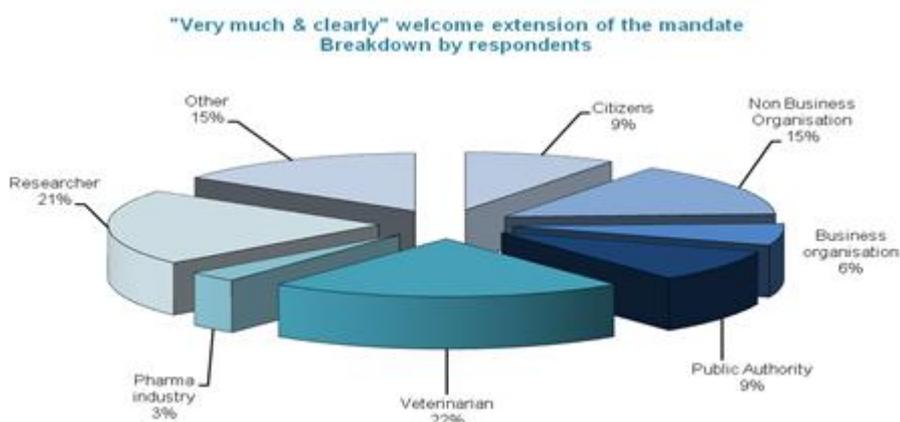
It was suggested that TATFAR would be of added value as a platform for exchange of views, best practices and better alignment of the EU and US initiatives, policies and regulatory measures against AMR, including cooperation in the fields of:

- Prudent use of therapeutic use in human and veterinary medicines:
 - Exchange of views and best practices;
 - Surveillance;
 - Awareness and communication;
 - Animal production models;
 - Off-label use of antibiotics;
 - Development and use of diagnostic tools.
- Infection control:
 - Exchange of best practices.
- Strategies to improve the pipeline of new antimicrobial drugs:
 - Exchange of best practices;
 - Greater alignment in regulatory procedures and requirements regarding new antibiotics;
 - Harmonised data requirement between Europe and US;
 - Harmonised and transparent licensing standards.

3. Support for extension of the mandate of TATFAR

Pending a review of the first outcomes of TATFAR, the majority of respondents would welcome an extension of the mandate of the taskforce to ensure long-term commitment against AMR.

| Would you welcome extension of the mandate of TATFAR beyond 2011? | Number of responses | % of total |
|---|---------------------|------------|
| Not at all | 1 | 2.2% |
| Not much | 0 | 0% |
| Somewhat | 11 | 24.4% |
| Clearly | 12 | 26.7% |
| Very much | 16 | 35.6% |
| Do not know | 3 | 6.7% |



4. Suggestions for the future

Some participants stressed the need to consider, in case of the extension of this mandate:

- broadening the geographical scope of the initiative; and
- the necessity to ensure a better involvement of the stakeholders in the activities of the taskforce.

The full report is available at the following [link](#) along with further information on the replies received, etc.

OGHA HHS public listening session

Meeting summary, 7 June 2010

- TATFAR representatives present: Mary Lisa Madell (HHS), Ed Cox (FDA), Jane Knisely (NIH/NIAID)
- Commenters: Janet Shoemaker (ASM), Ashley Shelton (AVMA), Leslie McGorman (IDSA), Kathleen Young (APUA)

Janet Shoemaker, Director of Public Affairs, American Society for Microbiology (ASM)

- ASM hopes that the taskforce can:
 - Engage with industry to provide the necessary incentives to develop new drugs and diagnostics (the pipeline);
 - Learn from each other on the key areas of surveillance, research, education and prevention.
- ASM looks forward to working with the taskforce and would be happy to help in any way that they can.

Ashley Shelton, American Veterinary Medical Association (AVMA)

- TATFAR is an opportunity to promote collaboration between human and animal communities.
- AVMA supports incentives for drug development.
- AVMA seeks ways to work collaboratively with TATFAR.

Leslie McGorman, Infectious Diseases Society of America (IDSA)

- Hopes that the taskforce can facilitate IDSA's 10x20 initiative.
- IDSA believes that this issue must be addressed in a global framework with input from all stakeholders.
- IDSA recommends that:
 - A TATFAR chairperson be announced;
 - The TATFAR have non-government members or outside advisory boards;
 - The TATFAR convene further opportunities for public consultation.

Kathleen Young, Executive Director, Alliance for the Prudent Use of Antibiotics (APUA)

- The TATFAR is a uniquely powerful group with access to significant leverage points and funding sources.
- Outcome should not be another report on the state of AMR, but should be an implementation plan of solutions identified by previous reports (25 reports were identified by APUA).
- APUA suggested TATFAR focus on the two following broad areas:
 - Reduce unnecessary selective pressure:
 - Surveillance – need a harmonised approach and the collection of sound baseline data;
 - Infection control – needs to be combined with antimicrobial stewardship;
 - Antimicrobial use on farms needs to be addressed.
 - Promote novel technologies (diagnostics, new drugs, alternative therapies and infection control measure):
 - Research is still needed into basic questions – formulate a coordinated research agenda for the basic science of AMR;
 - Consider designating antimicrobials as a special class of drugs (i.e. orphan drug).
- APUA believes that cooperation between government and private sector is necessary to address this issue.

In addition to the comments presented at the public listening session, further comments were submitted in writing, including written versions of the comments presented at the listening session. Comments were received from Rachel Nugent, Chair, Working Group on Drug Resistance, Center for Global Development; Dr. Andreas Heddini, Executive Director and Dr. Anthony D. So, Strategic Policy Director, ReAct – Action on Antibiotic Resistance; and Maya Sequeira, Communications Coordinator, Center for Disease Dynamics, Economics & Policy, Resources for the Future.

Rachel Nugent, Chair, Working Group on Drug Resistance, Center for Global Development

Ms. Nugent provided specific suggestions for consideration by the task force:

- Globalize the TATFAR by promoting global awareness through support of WHO's 2011 World Health Day theme of antimicrobial resistance and taking steps to conform Antimicrobial Awareness Day in the United States and European Union, and then globally.
- Recognize cross-disease resistance: drug resistance affects the ability to effectively treat all major infectious diseases by seeking opportunities to promote and support cross-disease responses, such as surveillance, laboratory capabilities, and appropriate dispensing and use of drugs, and support the Working Group's recommendation for a bi-annual Global Drug Resistance Report to compile available data about drug resistance in one place.
- Focus research on resistance mechanisms by examining strategies for improving the pipelines of resistance-specific technologies, beyond simply new drugs.
- Encourage and participate in partnerships by stimulating and joining partnerships, especially to encourage appropriate use of medicines globally, including being open and inclusive in conducting its own work.

Dr. Andreas Heddini, Executive Director and Dr. Anthony D. So, Strategic Policy Director, ReAct – Action on Antibiotic Resistance

Drs. Heddini and So stated that the fight against antimicrobial resistance will require context-specific approaches, highly innovative financing mechanisms and new models for research and development. The magnitude of the problem necessitates concerted global action to provide new technologies and conserve existing drugs. They directed the attention of the TATFAR to a recent open letter from ReAct which outlined a proposal to reframe strategic and policy approaches to antimicrobial resistance and recommended strategies for encouraging innovation and developing context-specific models for the rational use of antibiotics and infection control. They also highlighted an op-ed piece in the British medical Journal (BMJ 2010;340:c2071) which pointed out the need to develop new models of research and development.

Maya Sequeira | Communications Coordinator, Center for Disease Dynamics, Economics & Policy, Resources for the Future

Ms. Sequeira welcomed the creation of the TATFAR and recommended that its scope extend beyond just the United States and the European Union, reflecting the global scale of the problem of antibiotic resistance, which has largely gone unnoticed in low- and middle-income countries. Resources for the Future expressed the view that drug development is not sufficient, and that it is also important to extend antibiotic effectiveness by way of vaccination, infection control, judicious prescribing, promotion of antibiotic alternatives and investment in novel therapies combined with incentives not to oversell these drugs. The focus should be on policies that treat antibiotic effectiveness as a vital resource to be conserved and protected.

OGHA HHS public meeting

Meeting summary – 1 October 2010

The Office of Global Health Affairs hosted a public meeting for comment on the activities of the TATFAR. The meeting was led by US Chair Dr Nils Daulaire, Director of the Office of Global Health Affairs, HHS. US TATFAR members from FDA, CDC and NIH/NIAID were also in attendance. Following introductions of the US taskforce members, Dr Daulaire provided an overview of the current status and mandate of the TATFAR. After Dr Daulaire's presentation, the session was opened for public comment.

Dr Jared Silverman, Vice President for Discovery Biology, Cubist Pharmaceuticals

Dr Silverman outlined recommendations for the taskforce to consider. His recommendations stressed the need for incentives to enhance research and development in the area of antibiotics and are as follows:

1. Enhance market and data exclusivity for qualified infectious disease products. He encouraged linking this exclusivity to drugs for human use only. This would enable companies to make a profit even with strict stewardship guidelines that should accompany any new antimicrobial.
2. Authorise studies of the effectiveness of guaranteed market contracts and other "pull" market mechanisms, such as those outlined in the London School of Economics report.
3. Create infectious disease product development grants targeting the clinical development of innovative antibiotics. In response to a question, Dr Silverman indicated that these grants could be similar to those used by the Department of Defense for clinical trials of drugs that could be used in response to biological weapons.

Dr Allan Coukell, Pew Health Group

His presentation focused on 1) preserving the effectiveness of existing antimicrobials, and 2) promoting the development of new drugs. He stated that resistance to antibiotics is fuelled by injudicious use of existing drugs and is compounded by a failure to invest adequately in the development of new ones. A proposed way forward outlined in Dr Coukell's presentation recommended strategies from the Institute of Medicine (2003) consensus report, "Microbial Threats to Health: Emergence, Detection and Response". The recommendations are: 1) Limit antimicrobial use to therapeutic situations, 2) Discourage misuse, 3) Reduce the need for antibiotics by practicing prevention, and 4) Develop policies and incentives aimed at innovation. Dr Coukell had a few specific recommendations of areas that could prove fruitful for TATFAR collaboration.

1. Issue best practice guidelines on the use of antimicrobials in agricultural settings, drawing from experiences on both sides of the Atlantic.
2. Aid companies willing to undertake clinical development of novel antimicrobial products by collaboratively funding 1) the development of validated outcome measures that could be used as endpoints in clinical trials, and 2) the development of effective diagnostic tests that could be instrumental in streamlining patient enrollment. Both of these measures could help reduce the costs of clinical development. He stated that incentives need to reflect the variety of pathways for development – large companies, small companies, university laboratories – and that each would require different incentives. A small company may need assistance in negotiating the regulatory process or meeting the costs of regulatory approval, whereas a large company may benefit from a tax break.

Dr Rachel Nugent, Deputy Director for Global Health, Center for Global Development (CGD)

While Dr Nugent recognised that the taskforce deals specifically with a mandate between the US and the EU, she felt that the TATFAR could be instrumental in raising awareness about this global health issue.

Dr Nugent highlighted two specific recommendations from the recent CGD report, "The Race Against Drug Resistance", that have relevance to the work of the TATFAR:

1. TATFAR could partner with CGD in a proposed global partnership to improve drug prescribing, dispensing and use. This should include providing assistance to developing countries on interventions that improve prescribing, dispensing and use that they could use in their settings. In addition, the United States and the European Union could harmonise their respective national campaigns. In addition, Dr Nugent stated that linking the available information on surveillance for resistance would be useful, through a network of drug resistance surveillance networks. A process that reported on surveillance findings every two years would motivate countries to take action to improve their surveillance.
2. TATFAR could partner in a proposed web-based drug resistance marketplace to share resistance-specific research and innovation across diseases and creating a market place to encourage research collaboration.

Following the comments Dr Daulaire stated that this meeting was not the only opportunity for the public to comment on the work of the taskforce, and informed the meeting participants that their recommendations would be considered. He also encouraged the participants continue to follow the work of the TATFAR.

In addition to the comments presented at the public meeting, further comments were submitted in writing, including written versions of the comments presented at the meeting. Comments were received from Kathleen T. Young, Executive Director, and Dr. Stuart B. Levy, President, Alliance for the Prudent Use of Antibiotics.

Kathleen T. Young, Executive Director, and Dr. Stuart B. Levy, President, Alliance for the Prudent Use of Antibiotics (APUA)

APUA, a global scientific and public health organization which promotes evidence-based policies to improve antimicrobial access through multidisciplinary research, noted the high costs of antibiotic resistance. A recent APUA study at Cook County Hospital found that antibiotic resistance cost the hospital \$20 billion annually. APUA suggests the Task Force focus on 2 main goals over the next 12-15 months: 1) Reduce unnecessary selective pressure on existing antimicrobial agents and 2) Promote the development of new antibiotic products.

APUA outlined ways in which these goals can be accomplished.

1. Develop and publicize a concrete "emergency action plan"
2. Ensure surveillance systems to monitor antibiotic use and resistance
3. Reduce antibiotic misuse on the farm
4. Promote infection control programs and antibiotic stewardship programs
5. Research funding and incentives to promote new products
6. Designation of antibiotics as a special class of drugs

Annex G – TATFAR rosters

TATFAR members

| TATFAR members | | |
|---|---------|----------------------|
| United States delegation | | |
| HHS | US | Nils Daulaire |
| HHS | US | Mary Lisa Madell |
| CDC | US | Denise Cardo |
| CDC | US | Jean Patel |
| CDC | US | J. Todd Weber |
| NIH/NIAID | US | Dennis Dixon |
| NIH/NIAID | US | Jane Knisely |
| FDA | US | Edward Cox |
| FDA | US | Linda Tollefson |
| European Union delegation | | |
| EC – DG SANCO | EU | Andrzej Rys |
| EC – DG SANCO | EU | Nabil Safrany |
| EC – RTD | EU | Anna Lönnroth Sjöden |
| EMA | EU | David Mackay |
| EFSA | EU | Marta Hugas |
| ECDC | EU | Dominique L. Monnet |
| EU Presidency trio representatives | | |
| Scientific Institute for Public Health | Belgium | Boudewijn Catry |
| Office of the Chief Medical Officer | Hungary | Emese Szilágyi |
| Health Institute Carlos III | Spain | José Campos |
| Secretariat | | |
| ECDC | Sweden | Sarah Earnshaw |
| ECDC | Sweden | Andrea Mendez |

Working groups: Chairs, co-chairs and members

Working group 1 – Appropriate therapeutic use of antimicrobial drugs in human and veterinary medicine

Subgroup on human medicine

| | |
|----------------------------|---|
| Dominique L. Monnet | ECDC – Chair |
| J. Todd Weber | CDC – Co-chair |
| Anna-Pelagia Magiorakos | ECDC |
| Arjun Srinivasan | CDC |
| Boudewijn Catry | Scientific Institute for Public Health, Belgium |
| David White | FDA |
| Denise Cardo | CDC |
| Lauri Hicks | CDC |
| Marc Struelens | ECDC |

| | |
|--------------------|--------------------|
| Marco Cavaleri | EMA |
| Melinda Neuhauser | CDC |
| Nabil Safrany | EC – DG SANCO – C3 |
| Norbert Schnitzler | BfArM, Germany |
| Sarah Earnshaw | ECDC |

Sub-group on veterinary medicine

| | |
|--------------------------|---|
| Koen Van Dyck | EC - DG SANCO – G4 – Chair |
| Linda Tollefson | FDA – Co-chair |
| Boudewijn Catry | Scientific Institute for Public Health, Belgium |
| David White | FDA |
| Ernesto Liebana | EFSA |
| G rard Moulin | AFSSA, France |
| J. Todd Weber | CDC |
| Jean-Charles Cavitte | EC – DG RTD – E4 |
| Jordi Torren | EMA |
| Kris De Smet | EC – DG SANCO – G4 |
| Leena R s nen | EC – DG SANCO – G4 |
| Pierre-Alexandre Beloeil | EFSA |
| Tom Chiller | CDC |

Working group 2 – Prevention of drug-resistant infections

| | |
|----------------------------|-----------------------------|
| Denise Cardo | CDC – Chair |
| Dominique L. Monnet | ECDC – Co-chair |
| Anna-Pelagia Magiorakos | ECDC |
| Antoon Gijssens | EC – DG SANCO – C3 |
| Carl Suetens | ECDC |
| Carlo Gagliotti | ECDC |
| Cliff McDonald | CDC |
| Fernanda Lessa | CDC |
| Jean Patel | CDC |
| John Jernigan | CDC |
| Jos  Campos | Health Institute Carlos III |
| Klaus Weist | ECDC |
| Marc Struelens | ECDC |
| Matt Moore | CDC |
| Ole Heuer | ECDC |
| Scott Fridkin | CDC |

Working group 3 – Strategies for improving the pipeline of new antimicrobial drugs

| | |
|----------------------|----------------------------------|
| Edward Cox | FDA – Chair |
| Mair Powell | MHRA , UK– Co-chair |
| Anna Lönnroth Sjöden | EC – DG RTD |
| Arjon van Hengel | EC – DG RTD |
| Dennis M. Dixon | NIH/NIAID |
| Emese Szilágyi | National Center for Epidemiology |
| Jane Knisely | NIH/NIAID |
| John Farley | OND/CDER/FDA |
| Jordi Llinares | EMA |
| Katherine Laessig | OAP/OND/CDER/FDA |
| Lillian Abbey | NIH/NIAID |
| Marco Cavaleri | EMA |
| Martinus Nagtzaam | EC – DG SANCO |
| Rosemarie Aurigemma | NIH/NIAID |

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<http://ecdc.europa.eu/en/activities/diseaseprogrammes/tatfar/pages/index.aspx>

For direct enquiries or questions, contact the TATFAR Secretariat at tatfar_secretariat@ecdc.europa.eu

