



# Transatlantic Taskforce on Antimicrobial Resistance: Progress report

May 2014

**Recommendations for future collaboration  
between the US and EU**

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## Foreword

Antimicrobial Resistance (AMR) is a public health problem of increasing magnitude and importance recognized by the United States (US) and the European Union (EU), as well as their partner countries. Resistance occurs naturally, but misuse and overuse is rapidly increasing the prevalence of hard to treat infections in both humans and animals. At the current pace AMR is developing and given the lack of new antimicrobial drugs in development, we could foresee a future in which our grandchildren may once again begin to die from complications of a mundane infection from a skinned knee or in which patients no longer consistently survive routine surgeries. Without the ability to heal infections, medically innovative procedures may be beyond our reach. Antimicrobial drugs are tools that have empowered us to push the boundaries of our knowledge, and without them, the progress that has defined healthcare in the 20<sup>th</sup> and 21<sup>st</sup> centuries may be stymied or regress.

Recognizing that AMR is a growing and dangerous public health issue, US President Obama and then-President of the EU, Prime Minister Fredrik Reinfeldt from Sweden, established a transatlantic taskforce on antimicrobial resistance (TATFAR) on the margins of the US-EU summit in 2009. In September 2011, 17 recommendations on AMR were put forth to articulate future collaborations between the US and EU. These recommendations fall into three broad categories: urgent AMR 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. TATFAR has led to fruitful cooperation between the US and EU that has begun to make a tangible difference in the fight against AMR.

Based on the promise shown by our early cooperation, we decided to renew TATFAR in 2013 for another two-year term. In addition, we agreed to transfer the Secretariat from the European Centre for Disease Prevention and Control (ECDC) to the US Centers for Disease Control and Prevention (CDC) for the renewal term. As TATFAR moved into its two-year renewal period, this report reviews the progress that has been made for each recommendation and feedback to determine whether work toward the recommendation should continue in the future. Work on 15 of the original TATFAR recommendations and one new recommendation will continue into 2015, a strong testament to the benefits of the cooperation between the US and EU.

Continuous effort is needed at global and national levels to develop a cross-sectorial approach spanning human health, agriculture, food safety, and infection control in healthcare settings to effectively contain AMR. Both the US and EU look forward to further, expanded cooperation by working together to meet the present and ever-evolving challenges presented by AMR.



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## Executive summary

The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was created in 2009 with the goal of improving cooperation between the US and the EU in three key areas: appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities, prevention of healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs. TATFAR identified and adopted 17 recommendations for future collaborations between the US and the EU. The implementation of the recommendations has been carried out through increased communication; regular meetings and joint workshops; and exchange of information and approaches, best practises and methods.

This report summarises the progress and the outcomes of the implementation of the 17 recommendations, as well as the decision about the future of each recommendation. In addition, it also includes one new recommendation.

Each of the recommendations increased communication and collaboration between EU and US partners. In addition, the following outputs have been generated or are expected as a result of the first TATFAR period (2011-2013):

- A report summarising the results of a review that identifies a minimum set of common indicators to include in the US and the EU country strategies on hospital antimicrobial stewardship is expected by September 2014 (recommendation 1);
- A joint publication summarising the results of a review of the existing methods for measuring antimicrobial use in hospital settings is expected by September 2014 (recommendation 2);
- A joint publication on the comparison of the results of the U.S and EU point prevalence survey on healthcare-associated infections and antimicrobial use in European acute care hospitals is expected by December 2014 (recommendation 7);
- Adoption of Term of References for transatlantic communication of critical events that may signify new resistance trends that have global public health implications (recommendation 8);
- A joint publication describing the current status and evolution of infection control programmes in the EU and in the US (recommendation 10);
- A joint publication delineating the need for new vaccines for HAIs and which vaccines are most needed expected by November 2014 (recommendation 11);

- A report on the 2011 workshop, “Challenges and solutions in the development of new diagnostic tests to combat antimicrobial resistance” has been published on the [TATFAR website](#) (recommendation 13);
- Joint presentations to the scientific community to increase awareness on and promote the available funding opportunities on both sides of the Atlantic will continue (recommendation 14).

Collaboration between the US and the EU has led to an increase in exchanging information, understanding of best approaches and practices, and developing peer relationships. While significant progress has been made, concern related to AMR continues to grow. Therefore, the mandate of the taskforce has been extended for two additional years. The collaboration on, and the implementation of, 15 recommendations will continue as previously defined, one recommendation has been added, and two recommendations will cease as the path for future collaboration was not clear.

## Introduction

### Background on 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<sup>1</sup> agents have become available, many of which have been rendered ineffective by the remarkable ability of bacteria to become resistant through 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 antimicrobial drugs has resulted in drug resistance that threatens to undermine the tremendous life-saving power of these drugs.

AMR 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 antimicrobial drugs for some infections—a future in which 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 that 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. Patients 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. Furthermore, infections caused by drug-resistant organisms have a financial burden because of increased costs associated with additional doctor visits, longer hospital stays, more expensive drugs and treatment options, and productivity losses. Although the total economic cost of AMR is difficult to calculate, in 2009, the ECDC and The European Medicines Agency (EMA) estimated that the overall cost for the EU in terms of extra health care costs and productivity losses totaled at least EUR 1.5 billion each year<sup>1</sup>. For the US,

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<sup>1</sup> Antimicrobial drugs are used to treat infections caused by a wide range of infectious agents including viruses, fungi, and parasites, whereas antibacterial or antibiotic drugs are a subset of antimicrobial drugs used to treat bacterial infections. The TATFAR activities are focused on antibacterial resistance and consideration of this focus should be given wherever “antimicrobial” is used in this report.

estimates are as high as \$20 billion in excess direct health care costs, with additional costs to society for lost productivity as high as \$35 billion a year<sup>2</sup>. 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 23 000 deaths in the US<sup>2,3</sup>. 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<sup>1,4</sup>.

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<sup>1,3,5</sup>. In the setting of continued development of AMR and an insufficient pipeline to supply new options, the problem of AMR has become more pronounced. Because of the time and expense required to bring a new drug from the point of discovery to the market place, we need to respond to the current situation and 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 emergence and spread of Carbapenem-Resistant Enterobacteriaceae (CRE), such as gram-negative bacteria carrying the New Delhi Metallo beta-lactamase (NDM)<sup>6</sup> or *Klebsiella Pneumoniae* Carbapenemase (KPC) resistance genes, are particularly worrisome because carbapenems are one of the last line antibiotic drugs to treat MDR infections. In the US, an estimated 9 300 health care-associated infections (HAIs) caused by CRE occur, and infections caused by carbapenem-resistant *Klebsiella* spp. and carbapenem-resistant *Escherichia coli*, the two most common types of CRE, lead to approximately 600 deaths each year<sup>7</sup>. The Europe-wide point prevalence survey (PPS) of HAIs and antimicrobial use in European acute-care hospitals (2011-2012) estimated that 3.2 million HAIs occur each year in the EU, of which 51 901 are associated with carbapenem-non-susceptible Enterobacteriaceae (including *Klebsiella* spp., *E. coli*, *Enterobacter* spp., and *Proteus* spp.) and 46 702 are caused by carbapenem-non-susceptible *Acinetobacter* spp.<sup>8</sup>. The rapid spread of carbapenem-resistant bacteria is a serious threat to health care and patient safety worldwide. The consequence of infections with these bacteria is fewer treatment options, resulting in increased disease and death. Given that few novel antimicrobial agents are likely to become available for clinical use in the short- to medium-term, the risks that AMR poses to public health are not difficult to fathom.

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<sup>2</sup> ECDC/EMA Joint Technical Report: The bacterial challenge: time to react. 2009.

<sup>3</sup> CDC Report: Antibiotic resistance threats in the United States, 2013.

<sup>4</sup> Boucher, HW et. al. 2009. Bad Bugs, No Drugs: No ESCAPE! An Update from the Infectious Diseases Society of America. Clin Infect Dis 48(1): 1-12

<sup>5</sup> 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](http://www.se2009.eu/polopoly_fs/1.16814!menu/standard/file/LSE-ABIF-Final.pdf). September 2009.

<sup>6</sup> Walsh T et al. Int J Antimicrob Agents. 2010, Suppl 3: S3-14.

<sup>7</sup> CDC Report: Antibiotic resistance threats in the United States, 2013.

<sup>8</sup> <http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf>



In addition to their central role in human medicine, antimicrobial drugs 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 in some regions (e.g., to enhance growth, improve feed efficiency). In contrast to human medicine in which treatment is usually directed toward an individual patient, entire groups of animals may be treated by the use of medicated feed and water. As a result of continued exposure to antimicrobial drugs, the prevalence of resistant bacteria in the faecal flora of food animals may be relatively high. Determining the impact of these resistant bacteria on human infections is an ongoing challenge as many classes of antimicrobial drugs 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 (seafood production).

Developing new drugs alone will not be sufficient to address the growing resistance problem. Microbes will always find a way to overcome the therapeutic effect of new drugs; therefore, the efficacy of existing drugs needs to be preserved. Promoting the appropriate use of antimicrobial agents—use that maximises therapeutic effect while minimising the development of AMR—in both human and veterinary medicine is key to reducing selective pressure that leads to the development of resistance. Preventing infections, including through vaccination, is essential to control the spread of infectious diseases and their associated resistance factors. Another way to decrease selective pressure on bacteria in the gut and the environment is to use drugs with a narrow spectrum of activity or alternative therapeutic approaches that do not exert selective pressure. This type of targeted treatment will remain limited until 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 eligible patients to be identified efficiently.

## **History and scope of the Transatlantic Taskforce on Antimicrobial Resistance (2009-2013)**

### **Establishment of the TATFAR**

The growing global threat of AMR 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 AMR issues focused on three key areas: 1-appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, 2-prevention of both health care- and community-associated drug-resistant infections, and 3-strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us.” The TATFAR was constituted on the basis of this declaration.

### **Composition of the TATFAR**

Membership of the TATFAR is restricted to US government employees and EU civil servants. Nine members from each side of the Atlantic were selected on the basis of the areas of expertise identified in the summit declaration. A roster of the TATFAR members can be found in Annex B.

### **Scope of the TATFAR**

AMR is a diverse issue with numerous contributing factors. The work of the TATFAR primarily focused on the specific areas identified in the summit declaration. The scope and term of references of TATFAR are described in Annex C.

### **Working structure of the TATFAR**

The initial primary task of the TATFAR was to define specific areas in which 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.

### **Recommendations for future collaboration between the US and EU**

Through regular meetings and several public consultations, the members of the TATFAR identified a set of 17 recommendations in these key areas for future collaboration between the US and EU. The recommendations were adopted on 22 September 2011 and are described in Annex D.

### **Implementation of the recommendations for future collaboration between the US and EU**

Upon adoption of the 17 recommendations for future collaboration between the US and EU, the TATFAR began the process of implementation them. To implement the recommendations, working groups were composed and lead agencies, TATFAR implementers, and contributors were chosen.

The first TATFAR mandate was set for two years (2011-2013). The timeline and key dates of TATFAR are summarised in Annex E.

### **Review of implementing recommendations and future of the TATFAR**

After this period (2011-2013), TATFAR reviewed the implementation of the 17 recommendations and decided that 15 recommendations would continue to be implemented, although some will have a modified scope. Two recommendations will cease, and one recommendation has been added. On 3 December 2013, the mandate of TATFAR was extended for an additional two years.

## Recommendations

### Key Area I. Appropriate therapeutic use of antimicrobial drugs in human and veterinary medicine

#### Background

Antimicrobial drugs are critical to human and veterinary health and must be used appropriately to avoid unnecessary resistance from developing. Nearly 50% of antimicrobial use is unnecessary, inappropriate, or not optimally effective as prescribed<sup>9,10</sup>. Common types of inappropriate use include prescription of antibacterial drugs for viral infections and use of broad-spectrum antimicrobial drugs to treat infections in which narrow-spectrum drugs are recommended. In November 2013, an EU-wide survey showed that 49% of Europeans believed that antibiotic drugs kill viruses and 41% believed that they are effective against colds and the flu<sup>11</sup>; therefore, patient expectations may contribute to inappropriate use of antibiotic drugs in outpatient settings. Furthermore, a recent study found an upward trend in the use of broad-spectrum antimicrobial drugs to treat acute respiratory infections in which narrow-spectrum drugs are recommended<sup>12,13</sup>. The overuse of antibiotic drugs is contributing to the growing challenges posed by *Clostridium difficile* in many healthcare facilities, as well as the emergence of new resistance genes. Studies demonstrate that improving the use of antibiotic drugs in hospitals can not only help reduce rates of *C. difficile* infection and antibiotic resistance, but can also improve individual patient outcomes while substantially reducing health care costs<sup>14</sup>. To combat inappropriate use of antibiotic drugs, antimicrobial stewardship programmes and campaigns to promote adherence to treatment guidelines are critical in preserving the effectiveness of existing antimicrobial drugs. Both CDC and ECDC are active in these key areas; see Annex F 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, task forces, and organisations have studied and published on the matter, beginning with the Swann Report in 1969. In 1997, the World Health Organisation (WHO) published the first of several reports on this issue, The Medical Impact of Antimicrobial Use in Food Animals<sup>15</sup>. In 2000, a WHO expert consultation resulted in WHO Global Principles for the Containment of Antimicrobial Resistance in Animals

<sup>9</sup> Dellit T et al. Clin Infect Dis (2007) 44(2):159-177.

<sup>10</sup> CDC Report: Antibiotic resistance threats in the United States, 2013.

<sup>11</sup> [http://ec.europa.eu/health/antimicrobial\\_resistance/docs/ebs\\_407\\_en.pdf](http://ec.europa.eu/health/antimicrobial_resistance/docs/ebs_407_en.pdf)

<sup>12</sup> Kronman M et al. Pediatrics (2011) 127;3, 411-417.

<sup>13</sup> <http://pediatrics.aappublications.org/content/early/2013/11/12/peds.2013-3260.full.pdf+html>

<sup>14</sup> Kallen A et al. Infect Control Hops Epidemio (2009) 30(3):264-72.

<sup>15</sup> [http://whqlibdoc.who.int/hq/1997/WHO EMC\\_ZOO\\_97.4.pdf](http://whqlibdoc.who.int/hq/1997/WHO EMC_ZOO_97.4.pdf)

Intended for Food<sup>16</sup>. During the same time period, many reports on the topic were published by European and American scientists, deliberative bodies, and government agencies. Some recommendations appear repeatedly in these reports, including: support for continued monitoring of resistance among bacteria from food animals and food of animal origin and continued monitoring of use of antimicrobial drugs, and the promotion of responsible use of antimicrobial drugs; and requiring veterinary oversight of all antimicrobial drugs use in animals.. To tackle these issues, the US Food and Drug Administration (FDA), EMA, and the European Food Safety Agency (EFSA) work actively in these key areas; see Annex F for detailed descriptions of on-going programmes.

Both the EU and the US have been involved in international work on AMR in Codex Alimentarius, the WHO, 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.

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<sup>16</sup> [http://whqlibdoc.who.int/hq/2000/WHO\\_CDS\\_CSRAPH\\_2000.4.pdf](http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSRAPH_2000.4.pdf)

## *Areas of collaboration*

### ➤ **Antimicrobial stewardship in human medicine**

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

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

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

Antimicrobial stewardship is a coordinated programme that implements interventions promoting optimal antimicrobial prescribing to limit AMR and to prevent *C. difficile* infections, an adverse event associated with antibiotic use. Antimicrobial stewardship contributes to high quality and effective health care by decreasing unnecessary antimicrobial-related diseases, deaths, and costs. To effectively promote antimicrobial stewardship, an understanding of the key elements of successful stewardship programmes and interventions is needed. A common strategy for the use, monitoring, and interpretation of structure and process indicators of antimicrobial stewardship would allow meaningful comparisons between the US and EU Member States, as well as among institutions and regions.

ECDC and CDC reviewed the current available methods for evaluating hospital antimicrobial stewardship programmes in the EU and the US. Despite differences in the structure of and requirements for national programmes, ECDC and CDC agreed that a common structure and process indicators organized by functions of the stewardship programme's implementation and effectiveness should be developed, followed by a review of the scientific evidence supporting each of the proposed indicators. This review would ideally be based on the updated Cochrane Collaboration systematic review "Interventions to improve antibiotic prescribing practices for hospital inpatients"<sup>17</sup> (expected in 2014).

A meeting with key experts from ECDC and CDC, as well as external experts from the US and EU, is being discussed. The objective of this meeting would be to review selected structure and process indicators from the updated Cochrane Collaboration systematic review and to identify a minimum set of indicators that could be included in the US and the EU country strategies to allow

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<sup>17</sup> <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003543.pub3/pdf>

comparisons among institutions and regions. The results obtained through this review process will be summarised and presented in a final report (expected by September 2014).

**Future:** Activities under recommendation 1 will continue during the extension of TATFAR with the aim to identify a minimum set of common indicators to include in the US and the EU country strategies on hospital antibiotic stewardship.

### ➤ **Surveillance of antimicrobial use in human and veterinary communities**

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

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

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

Most human antimicrobial use occurs in healthcare settings. CDC and ECDC shared US and EU surveillance approaches and methods to measure antimicrobial use in these settings with the purpose of improving the comparability of the antimicrobial use data. This comparison requires synchronising data sources and methods (i.e. numerator) to generate common measures that can easily be compared (e.g., defined daily dose [DDD], days of therapy [DOT], etc.).

The National Healthcare Safety Network (NHSN) meeting in April 2012 (Jacksonville, Florida) and the 2<sup>nd</sup> ECDC meeting of the Antimicrobial Resistance and Healthcare-Associated Infections (ARHAI) networks in November 2012 (Berlin, Germany) provided the opportunity to review the measurement units and to identify the steps needed to synchronise methods or produce comparable data. A first joint US/EU expert meeting was held in June 2013 in Stockholm, Sweden, and focused on new ways to have additional types of measures and risk adjustments. A second joint US/EU expert meeting will take place in Spring 2014 (date to be confirmed) in Stockholm, Sweden, to finalise the review of existing methods for measuring antimicrobial use in hospital settings and to investigate whether comparable hospital level measures could be introduced in the EU and the US. The results and conclusions of these two meetings will be summarised in a scientific article (expected by September 2014).

**Future:** Activities under recommendation 2 will continue during the extension of TATFAR.

*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 antimicrobial drugs in food producing animals

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

Since the publication of the TATFAR report in 2011, FDA and EMA have been sharing information on the developing units for consumption of antimicrobial agents in food-producing animals. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project<sup>18</sup> has recently revised its considerations on collecting data on the use of antimicrobial agents per animal species, technical units of measurement, and indicators for reporting use of antimicrobial agents in animals<sup>19</sup>. This document discusses how to establish systems to collect reliable and standardised data on the use of antimicrobial agents by animal species for the ESVAC database and how to report the data, taking into account the differences in dosing between the various antimicrobial agents as well as the animal population. This reflection paper was prepared following a consultation period during which stakeholders provided input. This document and the annual reports<sup>20</sup> of the ESVAC project are regularly shared with FDA. The last ESVAC report includes data on the sales of veterinary antimicrobial drugs in 2011 in 25 EU/European Economic Area (EEA) countries and reveals that, although large differences in the sales and prescribing patterns are observed, some Member States reported a decrease in sales. Although it is premature to consider this change as representing a definitive trend, if it continues in future years, it could suggest that initiatives such as responsible-use campaigns, restrictions of use, and increased awareness in EU Member States are starting to have an impact in terms of reducing the overall sale of antimicrobial drugs in the veterinary sector. As a next step, ESVAC is working on the collection of use data by species as detailed in the above-mentioned reflection paper; the FDA and other stakeholders will be informed of the progress of this task.

FDA has exchanged views with EMA on current activities at the annual meeting of ESVAC project and has discussed data collection systems with representatives from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES). In 2012, FDA solicited broad public

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<sup>18</sup> ESVAC web page:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000302.jsp&mid=WC0b01ac0580153a00&jsenabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp&mid=WC0b01ac0580153a00&jsenabled=true)

<sup>19</sup> ESVAC reflection paper: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/12/WC500136456.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136456.pdf)

<sup>20</sup> European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2013.

'Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011' (EMA/236501/2013)  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/10/WC500152311.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500152311.pdf)



comment on enhancements to the existing requirements related to reporting antimicrobial drug sales/distribution data, as well as input on alternative methods for monitoring antimicrobial use in food-producing animals. In September 2013, FDA sought additional public input on a new proposed format for the annual summary and expects to use the enhanced format when it summarizes the data reported for 2012. Also, members of the EMA and FDA presented at the OIE Global Conference on the Responsible and Prudent Use of Antimicrobial Agents for Animals, which amongst other subjects addressed the collection of data on antimicrobial consumption in animals.

**Future:** Activities under recommendation 3 will continue during the extension of TATFAR. FDA and EMA will confer regularly to exchange updates on the status of efforts to collect data on sales and use of veterinary antimicrobial drugs in food producing animals.

### ➤ Risk analysis of foodborne antimicrobial resistance

*Issue: Methods for analysing the risk of AMR in foodborne pathogens vary widely*

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

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

FDA, EFSA, EMA, and DG SANCO are collaborating in order to implement the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance prepared by Codex Alimentarius<sup>21</sup>.

The FDA and EMA maintain regular bilateral meetings that include discussions on guidelines and recommendations for authorisation of antimicrobial drugs for use in veterinary medicine. A concept paper on a guideline for AMR risk assessment was adopted by The Committee for Medicinal Products for Veterinary Use (CVMP) at EMA; this concept paper will lead to a guidance document that will use as one of its pillars the previously mentioned Codex Alimentarius guidance and will include cross-reference to FDA guidelines<sup>22</sup> on risk assessment of antibiotic drugs.

During 2011, several reference documents related to antimicrobial drugs were produced by high-level authorities, including a report by the European Commission<sup>23</sup> and a guideline by the Codex

<sup>21</sup> Codex Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CAC/GL 77- 2011) [https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CEEQFjAA&url=http%3A%2F%2Fwww.codexalimentarius.org%2Finput%2Fdownload%2Fstandards%2F11776%2FCXG\\_077e.pdf&ei=ugmCUpxOe-N7AbPrYGIag&usq=AFQjCNGiZSR1bR815R-NJ7jzWDgmqW11UQ&bvm=bv.56146854.d.ZGU](https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CEEQFjAA&url=http%3A%2F%2Fwww.codexalimentarius.org%2Finput%2Fdownload%2Fstandards%2F11776%2FCXG_077e.pdf&ei=ugmCUpxOe-N7AbPrYGIag&usq=AFQjCNGiZSR1bR815R-NJ7jzWDgmqW11UQ&bvm=bv.56146854.d.ZGU)

<sup>22</sup> FDA guideline #152 (Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern) <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf>

<sup>23</sup> [http://ec.europa.eu/dgs/health\\_consumer/docs/communication\\_amr\\_2011\\_748\\_en.pdf](http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf)

Alimentarius Commission in the US<sup>24</sup>. More recently, a scientific opinion on carbapenem-resistance in food animal ecosystems from the BIOHAZ Panel in EFSA was published<sup>25</sup>.

The FDA, in collaboration with the Government of Costa Rica, conducted a workshop to discuss the implementation of the Codex AMR Guidelines in August 2012. Representatives from 16 Latin America countries attended this workshop. In addition, the FDA Center for Veterinary Medicine discussed FDA's strategy for addressing AMR issues, especially with regard to prudent use of antimicrobial drugs in veterinary medicine.

Much debate is currently focused on the extent to which AMR that occurs as a result of the use of antimicrobial drugs in food producing animals contributes to the overall risks to humans. Greater clarity on the scale and scope of transfer of resistance is essential to address gaps in our understanding of risks arising from different use practices. This information will ensure that appropriate control measures are put in place that balance the need to retain an adequate therapeutic arsenal to treat infectious diseases in animals against the need to limit the risk to humans.

**Future:** Activities under recommendation 4 will continue during the extension of TATFAR. The implementers will consider if additional activities to promote transatlantic cooperation in the area of controlling foodborne AMR could be initiated during this extension. In addition, on reviewing this recommendation, the implementers recognised that the extent and mechanisms of transmission of AMR from animals to man remain poorly understood. A new recommendation was therefore agreed specifically to identify and address the knowledge gaps in this area.

#### **New Recommendation:**

*Issue: Antibiotic use in animals can select for antimicrobial resistance that may represent a risk to man either through direct infection by resistant bacteria or by the transfer of resistance determinants to other bacteria.*

**Recommendation 18:** Establish a joint working group of international subject matter experts to identify key knowledge gaps in understanding the transmission to man of antimicrobial resistance arising as a result of the use of antimicrobial drugs in animals and on the development of effective intervention measures to prevent this transmission, including the development of alternatives to antimicrobial drugs.

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<sup>24</sup> Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CAC/GL 77- 2011)

<sup>25</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/3501.htm>

- Implementers: FDA, CDC, USDA, EFSA, EMA, ECDC, DG SANCO, and DG RTD
- Timeline: One year after adoption of recommendation

The impact that the use of antibiotic drugs in animals has on the risk to man from antimicrobial resistance needs to be better understood. The use of antibiotic drugs in animals selects for antimicrobial resistance; however, the mechanism by which this resistance may be transferred to man and the extent of the threat that this represents to human health is less clear. Likewise, different control strategies to limit the risk to man from the use of antibiotic drugs in animals have been developed and a wide variety of alternatives to the use of antibiotic drugs are under development and evaluation. Adopting a "one health" approach, whereby expertise is brought together from both the human and veterinary domains, the working group will consider all uses of antimicrobial drugs in animals and will examine the evidence linking the resistance arising as a result of this use to infections in man with resistant organisms. The group will consider existing control strategies to limit the emergence and spread of antimicrobial resistance as well as the development of alternatives to antimicrobial drugs. The working group will identify the gaps in knowledge that exist and will develop concrete recommendations for filling these knowledge gaps, including suggesting specific research studies.

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

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

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

EMA, DG SANCO, FDA, EFSA, and other stakeholders are working to enhance information sharing on approaches to promote appropriate use in veterinary communities.

Over the past few years, the CVMP at EMA has produced recommendations on prudent use with a particular emphasis on critically important antimicrobial drugs.

Information on prudent use is available on the EMA and FDA web sites and is regularly discussed and shared during bilateral discussions. Both EMA and FDA also collaborate with the WHO Advisory

Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) and OIE<sup>26</sup> on this topic; EMA has had additional engagement with WHO<sup>27</sup>.

In 2010, FDA announced a strategy to promote the judicious use of antimicrobial drugs in food-producing animals by phasing out production uses of antimicrobial drugs that are important in human medicine and phasing in veterinary oversight of the remaining therapeutic uses of these products. In December 2013, FDA implemented this strategy<sup>28</sup>, which recommends that drug sponsors phase in these changes over a three-year timeframe.

EMA is also providing evidence-based advice on the use of antimicrobial drugs in veterinary medicine, as requested by the European Commission (EC)<sup>29</sup>. The latest of those recommendations refer to the antibiotic drugs colistin and tigecycline<sup>30</sup>. The ESVAC project has noted during the last years that many of the participating countries have started to implement actions to promote responsible use of antimicrobial drugs in animals. In addition, EMA has started to consider the role that companion animals may play and the CVMP has therefore produced a reflection paper on the risk of AMR transfer to humans from companion animals<sup>31</sup>. This document addresses the risk for emergence and transmission of AMR from contact with companion animals (e.g., dogs, cats, horses, etc.) so that appropriate risk management measures can be adopted during authorisation of antimicrobial drugs for companion animals.

DG SANCO is finalising the drafting of the guidelines for prudent use of antimicrobial drugs in veterinary medicine. The purpose of the guidelines is to provide recommendations and practical guidance on the development of strategies and actions by Member States in order to promote and strengthen the prudent use of antimicrobial drugs, especially antibiotic drugs, in veterinary medicine. The Guidelines supplement existing legal provisions in the EU and, in order to make the recommendations as practical as possible, different EU Member States' approaches are provided as examples and possible sources of inspiration for other Member States.

**Future:** Activities under recommendation 5 will continue during the extension of TATFAR. The implementers will confer regularly to share approaches to promoting appropriate use in veterinary communities.

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<sup>26</sup> Oie Global Conference On The Responsible And Prudent Use Of Antimicrobial Agents For Animals  
[http://www.oie.int/eng/A\\_AMR2013/Recommendations.htm](http://www.oie.int/eng/A_AMR2013/Recommendations.htm)

<sup>27</sup>WHO booklet Tackling antibiotic resistance from a food safety perspective in Europe:  
[http://www.euro.who.int/\\_data/assets/pdf\\_file/0005/136454/e94889.pdf](http://www.euro.who.int/_data/assets/pdf_file/0005/136454/e94889.pdf)

<sup>28</sup><http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf>

<sup>29</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2013/04/WC500142070.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142070.pdf)

<sup>30</sup> Colistin [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/07/WC500146813.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146813.pdf) and tigecycline (glycylcyclines)  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/07/WC500146814.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146814.pdf)

## ➤ Campaigns to promote appropriate use in human medicine

*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

–Implementers: CDC and ECDC

–Timeline: Within two years of adoption of recommendation

Representatives from the US Get Smart Campaign and European Antibiotic Awareness Day have met through quarterly conference calls to develop joint priorities and share information about their respective work on prudent antibiotic use campaigns. These activities have focused on 4 key areas: (1) to share published and unpublished information assessing the evidence for effectiveness of communications tools in promoting behaviour change to increase appropriate use; (2) to share information regarding annual campaign development, including objectives, targets, strategies and evaluation; (3) to prepare joint initiatives promoting antibiotic awareness in the run up to Get Smart About Antibiotics Week/Antibiotic Awareness Day, (4) to identify opportunities for colleagues to participate in key educational meetings linked to promoting behaviour change to increase appropriate use.

Every year since 2010, CDC and ECDC agreed to launch both of their campaigns during the week of 18 November. Since 2012, Canada and Australia have also aligned the timing of their national prudent antibiotic use campaigns. In the area of social media, there have been several coordinated actions and joint activities since 2012, e.g., posting links on campaign websites and participation in the respective Twitter chats or joint tweets.

In 2013, ECDC and CDC published a joint editorial entitled “Global collaboration essential to spread the message on prudent antibiotic use” on prudent antibiotic use campaigns in the US and Europe, as well as in Canada and Australia in *Lancet Infectious Diseases*<sup>32</sup>. On 18 November 2013, both ECDC and CDC took part in the first extended global Twitter conversation with global partners (e.g., Canada and Australia). This Twitter conversation was based on a Twitter chat starting in Australia and ending on the west coast of North America using the same account and the same hashtag.

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<sup>32</sup> Earnshaw S et al. *Lancet Infect Dis.* 2013 Dec;13(12):1003-4.

**Future:** Activities under recommendation 6 will continue during the extension of TATFAR, Representatives from the US Get Smart Campaign and European Antibiotic Awareness Day will continue to discuss the coordination of annual joint activities and share lessons learned. With increasing calls for a Global Antibiotic Awareness campaign, ECDC and CDC will also consider broadening international participation in these campaigns, adding additional countries for this important collaboration on antibiotic drugs awareness.

## Key Area II. 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 most novel resistance factors first surface in healthcare facilities. Furthermore, resistant bacteria are also causing infections in the community with increasing frequency. The European-wide point prevalence survey of HAIs and antimicrobial use in European acute care hospitals (2011-2012) confirms that HAIs represent a major public health problem. ECDC estimates that on any given day, about 80 000 patients have at least one HAI (i.e., one in 18 patients in a European hospital has an HAI and one in three patients receive at least one antimicrobial agent on any given day<sup>33</sup>). Prevention of drug-resistant infections requires that the transmission of drug-resistant bacteria between patients 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 persons 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.

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<sup>33</sup> <http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf>

## *Areas of collaboration*

### ➤ **Surveillance of drug-resistant infections**

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

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

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

Since 2009, CDC and ECDC have attempted to harmonise key methods related to point prevalence surveys (PPS) of HAI and antimicrobial use. Although the ECDC and CDC protocols are not identical, additional variables were added to both protocols to enable comparison of results. CDC<sup>34</sup> and ECDC<sup>35</sup> completed their national PPS of HAIs and antimicrobial use in acute care hospitals in 2011 and 2012, respectively, providing national estimates of HAI rates and of antimicrobial use and information about the epidemiology of infections. During the process, CDC and ECDC also shared the preliminary results of their respective PPSs with each other. CDC and ECDC jointly presented the results of their PPSs at the symposium on “Are prevalence surveys still useful for healthcare-associated infections surveillance?” of the 52<sup>nd</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Conference (11 September 2012, San Francisco, US) and at the 2<sup>nd</sup> ECDC meeting of the antimicrobial resistance and healthcare-associated infections (ARHAI) networks (26-28 November 2012, Berlin, Germany). During the ECDC PPS evaluation meeting (17-18 September 2013, Stockholm, Sweden), CDC and ECDC agreed to further collaborate and discuss potential changes to the US and EU protocols for the future PPSs. CDC is considering conducting another PPS of HAIs and antimicrobial use in acute care hospitals in 2014-2015, and ECDC will organise a second EU-wide PPS in all EU Member States in 2016–2017. Furthermore, CDC is in the planning phase of a pilot prevalence survey of HAIs and antimicrobial use in nursing homes and is currently working with EU investigators to use a similar method as the ECDC-funded Healthcare-Associated Infections in Long-Term Care Facilities (HALT) project.

Differences in the sources of information and methods used in generating HAI burden estimates make drawing comparisons between the US and the EU data difficult at this time. A meeting bringing together key experts from ECDC and CDC to assess the differences in HAI epidemiology and priorities between the US and EU and their impact is under discussion. A major output for this

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<sup>34</sup><http://www.cdc.gov/hai/eip/antibiotic-use.html>

<sup>35</sup><http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf>



recommendation will be a joint publication on the comparison of the EU PPS results and the CDC PPS results (expected by December 2014).

**Future:** ECDC and CDC will continue to further discuss potential changes to the US and EU protocols for future PPSs.

*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

– Implementers: CDC and ECDC

– Timeline: Within two years of adoption of recommendation

Timely transatlantic communication and common actions are fundamental to respond to emerging threats and critical trends attributable to AMR. To allow for timely communication and for proper dissemination of information within the US, the EU, partner public health agencies, and ministries of health, CDC and ECDC drafted and approved terms of reference (ToR) on how international communication and actions about critical AMR surveillance results will occur and which type of information should be communicated. The ToR describes a procedure for notification when novel resistant phenotypes are identified, as well as quarterly conference calls in which CDC and ECDC subject matter experts discuss new AMR data and critical trends. These calls were initiated in 2012 and allow experts to exchange information on resistance but also on surveillance programs and protocols. As a result, each agency has gained better insight into the AMR situation and is fostering new collaborations. Topics that have been discussed include surveillance programs for resistant gram-negative bacteria, vancomycin-resistant *Staphylococcus aureus*, CRE, and drug-resistant *Neisseria gonorrhoeae*.

**Future:** Communication under recommendation 8 will continue as defined in the approved ToR during the two-year extension of TATFAR.

*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, interpretive criteria for susceptibility reporting of bacterial isolates across surveillance programmes in the US and EU

– 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

ECDC, CDC, EMA, FDA, and EFSA are using epidemiologic cut-off (ECOFFs) values for sensitive detection of acquired and mutational resistance in a variety of organisms (bacteria and fungi). ECOFFs distinguish between isolates with and without phenotypically detectable resistance mechanisms whereas clinical breakpoints distinguish between organisms that can and cannot be treated with the agent in question. ECOFFs can be used for the purpose of reporting harmonized surveillance results as described in this recommendation. The setting of ECOFFs requires standardised methods. In addition, for each organism and agent, MIC distributions from many investigators must coincide. TATFAR has agreed to encourage harmonisation of ECOFFs and MIC distributions of organisms of human, veterinary, and food safety importance. Criteria for a common MIC database and for the setting of ECOFFs need to be established. There is a need for swift progress since EFSA is already recommending the use of ECOFFs for measuring resistance in several pathogens and the U.S National Antimicrobial Resistance Monitoring System (NARMS) is adopting ECOFFs for reporting the results of *Campylobacter* monitoring beginning with data collected in 2012 and discussions are ongoing for adopting ECOFFs for reporting *Salmonella* results.

**Future:** Activities under recommendation 9 will continue during the extension of TATFAR.

### ➤ 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

–Implementers: CDC and ECDC

–Timeline: Within two years of adoption of recommendation

Hospital infection control programmes, which include effective infection control interventions, are critical to prevent and control the spread of bacteria, HAIs, and hospital outbreaks. Effective infection control programmes rely on good implementation of infection control measures, adequate training of healthcare professionals, and educational campaigns for healthcare professionals and the general public as well as the involvement of hospital administration.

CDC and ECDC reviewed the evolution of the culture of infection control in US and EU Member States and the available structure and process indicators for evaluating and monitoring hospital infection control programmes. The indicators used at the national and hospital programmes were not the same in the EU and the US, and facilities in the EU and US are at different stages in implementing infection control components. Furthermore, the US developed structures and process indicators linked to incentives and reimbursements, which are not common practises in the EU, with the exception of some EU Member States. Because the drivers and programmes in the US and in many EU Member States are different, CDC and ECDC agreed that reaching a consensus on common structure and process indicators for hospital infection control programmes would not be possible. The planned workshop was, therefore, cancelled and a joint peer-reviewed article was suggested. This article would describe the current status and evolution of infection control programmes in the EU and the US and would aim to raise awareness on this issue.

**Future:** Due to incompatibilities in the evaluation methods for hospital infection control programmes in the US and EU, activities under recommendation 10 will cease following completion of the article.

*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

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

Candidate vaccines to prevent infection with common HAIs, including MRSA and *C. difficile* have the potential to significantly reduce the prevalence of antimicrobial-resistant infections and associated diseases, deaths, and costs.

CDC and ECDC identified the existing initiatives to facilitate developing candidate vaccines to prevent infection with common HAIs. CDC and ECDC agreed to produce a joint peer-reviewed article delineating the need for new vaccines to address HAIs, including which vaccines are most needed and which patient populations would most benefit from different vaccines (expected by November 2014). This information can be used by vaccine developers as they select vaccine candidates, determine which patient populations to target, and design feasible clinical development programmes.

**Future:** Since CDC and ECDC use different models to interact with the vaccine industry, a common strategy could not be forged. Activities under recommendation 11 will cease.

## Key Area III. Strategies to improve the pipeline of new antibacterial drugs for use in human medicine

### *Background*

Government agencies on both sides of the Atlantic recognise the critical need for the development of new drugs to treat antimicrobial-resistant infections and are working to foster antibacterial research and development and facilitate the approval of new safe and effective antibacterial drugs through a variety of mechanisms. A number of factors contributing to the decline in antibacterial drug development have been discussed extensively<sup>36</sup>. A number of challenges are inherent to developing new antibacterial drugs. The recommendations describe specific efforts to overcome some of the challenges that are encountered when developing a new antibacterial drug to provide therapeutic options to treat patients' infections.

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 developing vaccines, drugs, and rapid diagnostic tests for resistant pathogens of concern. In addition, NIH/NIAID offers a broad array of preclinical and clinical services designed to fill gaps in drug development and lower the economic risk of antimicrobial drug development. At both the FDA and the EMA, effort has been invested in developing updated recommendations on the most appropriate clinical trial designs for evaluating antibacterial drugs. Several of these guidance documents were recently published and others are under development. More detailed descriptions of ongoing activities to stimulate antibacterial drug development pipeline can be found in Annex F.

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<sup>36</sup>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](http://www.se2009.eu/polopoly_fs/1.16814!menu/standard/file/LSE-ABIF-Final.pdf). September 2009.

## *Areas of collaboration*

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

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

**Recommendation 12:** Policymakers should strongly consider establishing significant incentives to stimulate antibacterial drug development.

Several meetings have been organised by different stakeholders around possible incentives to stimulate antibacterial drug development (e.g. Chatham House Conference on AMR, 3-4 October 2013, London, UK).

In the EU, in the context of the Innovative Medicines Initiative (IMI), a call has been launched for a project aimed at developing new business models for antibacterial drugs taking into consideration the option of delinking return on investment from sales volumes.

In the US, the Generating Antibiotic Incentives Now (GAIN) Act was signed into law in July 2012. GAIN provides for fast track designation, priority review, and additional marketing exclusivity in the US for certain qualifying antibacterial and antifungal drugs for the treatment of serious or life-threatening infections. FDA is collaborating with the Office of the Assistant Secretary for Planning and Evaluation of the Department of Health and Human Services on a study to evaluate the economics of antibacterial drugs, diagnostic devices, and vaccines for bacterial diseases and to evaluate the potential role of incentives to promote their development.

**Future:** FDA and EMA will continue to share information on new incentives available to drug developers on both sides of the Atlantic.

### ➤ **Research to support the development of new antibacterial drugs**

*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.

- Implementers: NIH and DG RTD
- Timeline: within one year of adoption of recommendation

Program officials from NIH/NIAID and DG RTD hold periodic teleconferences to exchange information on ongoing and planned programs and to identify areas in which further discussion and collaboration may be warranted. One such area identified during the initial stage of TATFAR was the development of rapid diagnostics to enable appropriate use of antimicrobial drugs, as well as more feasible antibacterial drug development programmes.

The Joint EU-US workshop “Challenges and Solutions in the Development of New Diagnostic Tests to Combat Antimicrobial Resistance” co-organised by the NIH/NIAID and the DG RTD, was held in September 2011. The workshop aimed to identify factors negatively impacting development, approval, introduction, and appropriate use of new diagnostic tools for invasive bacterial infections in both inpatient and outpatient settings. It also addressed the role of diagnostic tools in the development of novel antibacterial drugs and the challenges in development of companion diagnostics by drug developers<sup>37</sup>.

In conjunction with the 2013 European Society of Clinical Microbiology and Infectious Diseases meeting (ESCMID), NIAID coordinated discussions between NIH and EC-funded investigators conducting similar clinical trials on the optimal use of colistin for the treatment of MDR gram-negative infections. These trans-national discussions continued at the 1<sup>st</sup> International Conference on Polymyxins (2–4 May, 2013, Prato, Italy), which brought together US and EU investigators to share experiences with the polymyxins, including clinical trials designed to define their optimal use.

**Future:** NIH/NIAID and DG RTD will continue to share information about scientific priorities in the area of AMR and when appropriate, bring specific scientific communities together around specific research topics of particular interest.

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

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

- Implementers: NIH/NIAID and DG RTD
- Timeline: within one year of adoption of recommendation

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<sup>37</sup> [http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/news/Pages/TATFAR\\_Workshop.aspx](http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/news/Pages/TATFAR_Workshop.aspx)

Program Officials from NIH/NIAID and DG RTD have given two joint presentations at international meetings, the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) meeting (31 March–2 April 2012, London, UK) and the 1<sup>st</sup> International Conference on Polymyxins (2–4 May, 2013, Prato, Italy). During these presentations, resources available to investigators on both sides of the Atlantic, as well as the communication and collaboration efforts under TATFAR, were highlighted.

Additionally, efforts have been made to use the websites of NIH/NIAID, DG RTD, and TATFAR to publicise calls for proposals and other resources for researchers on both sides of the Atlantic. These efforts will be refined as the TATFAR website migrates from the ECDC-based system to the CDC-based system.

In 2012, the European Commission together with the European Federation of Pharmaceutical Industries and Associations, through their joint undertaking, the [Innovative Medicines Initiative](#) (IMI)<sup>38</sup>, launched “New Drugs for Bad Bugs” a major programme for combatting antibiotic resistance. This programme provides an avenue for leading academics, small and medium-sized enterprises, and major pharmaceutical companies to join forces to tackle AMR and to speed up the delivery of much-needed new antibiotic drugs to patients.

The Joint Programming Initiative on AMR (JPIAMR)<sup>39</sup>, launched in 2012, pools national research efforts to combat AMR within 17 European countries, Israel, and Canada. The JPI AMR has developed a strategic research agenda and issues transnational research calls.

In 2013, NIAID launched the Leadership Group for a Clinical Research Network on Antibacterial Resistance (ARLG), a major new AMR effort modelled after the NIAID HIV/AIDS Clinical Trials Networks. The ARLG has developed a [research agenda](#) identifying the most important clinical questions in antibacterial resistance, and [clinical studies/trials to address these questions are being solicited](#) from the global AMR research community.

**Future:** NIH/NIAID and DG RTD will continue to give joint presentations to the scientific community to make them aware of the numerous funding opportunities available to them. In addition, the new TATFAR website will provide convenient links to current and future funding opportunities in the US and EU.

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<sup>38</sup> <http://www.imi.europa.eu/>

<sup>39</sup> <http://www.imi.europa.eu/>



## ➤ Regulatory approaches for antibacterial products

*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 will discuss ways to facilitate the use of the same clinical development programme to satisfy regulatory submissions to both agencies

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

FDA and EMA have been discussing recommendations on clinical trial designs for studying new antibacterial drugs. Furthermore, EMA and FDA representatives have participated in meetings to address approaches to antibacterial drug development on both sides of the Atlantic. The two agencies have been engaged in providing scientific advice to drug developers to help outline programs that will satisfy requirements for the US and EU. EMA and FDA recommendations on clinical trial designs for studying new antibacterial drugs have been published in EMA's Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (2012)<sup>40</sup> and in a number of FDA guidance documents<sup>41</sup>.

**Future:** FDA and EMA will continue to work to facilitate the use of the same clinical development programme to satisfy regulatory submissions to both agencies.

*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

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

EMA and FDA have held periodic teleconferences focused on approaches to facilitate trials that are feasible, while ensuring the safety and efficacy of new antibacterial drugs, on at least a quarterly basis. In addition, joint EMA and FDA meetings and workshops focused on the exchange of information on options available to drug developers have taken place on both sides of the Atlantic.

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<sup>40</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003417.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003417.pdf)

<sup>41</sup><http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

**Future:** FDA and EMA will continue to hold regular meetings to discuss common issues in antibacterial drug development and regulation.

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

**Recommendation 17:** Exchange information on possible approaches for developing drugs for bacterial diseases if limited drugs are available (i.e., bacterial diseases for which insufficient antibacterial drug therapies are available often due to AMR)

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

FDA and EMA have exchanged information on possible approaches and each agency continues to update guidance documents on drug development programs for antibacterial drugs to address unmet medical needs.

In November 2013, EMA published the final “Addendum on the note for guidance on the evaluation of medicinal products indicated for treatment of bacterial infections,”<sup>42</sup> which includes recommendations on clinical trials and programs for development of antibacterial drugs for specific indications including for bacterial diseases for which there are limited therapeutic options for treating patients.

In July 2013, FDA published the draft guidance “Guidance for Industry Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases”<sup>43</sup>. The public comment for this draft guidance closed in October 2013, and FDA is working to evaluate the input received before developing the final guidance document on this topic.

In December 2013, members of the US Congress introduced legislation to establish a new development pathway for limited population antibacterial drugs (LPAD). LPAD drugs would be approved to treat limited populations of patients with serious or life-threatening manifestations of specific bacterial infections where few or no therapeutic options are available. The US Administration has not yet taken a position on the bill. However, FDA will work with Congress to provide technical assistance on legislation, as requested.

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<sup>42</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/07/WC500129443.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129443.pdf)

<sup>43</sup><http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf>

**Future:** FDA and EMA will continue to exchange information on possible approaches to developing drugs for patients for whom we have few therapeutic options.

## Conclusions

This report summarises the progress and the outcomes of the Transatlantic Taskforce on Antimicrobial resistance on the 17 recommendations that were identified to strengthen EU and US communication and cooperation in the area of AMR.

While significant progress has been made in the areas of appropriate therapeutic use of antimicrobial drugs in human and veterinary medicine, prevention of drug resistant infections and strategies to improve development of new antibacterial drugs for use in human medicine, AMR continues to escalate. Therefore, the work of the TATFAR will continue for a period of at least two years. Major outcomes, such as consensus papers, meeting reports, and periodic progress reports, will be posted on the TATFAR website.

Antimicrobial resistance is a growing and complex threat that requires sustained and coordinated action. Through the extension of the TATFAR mandate, the US and the EU reaffirm their commitment to working collaboratively through the TATFAR to address this priority public health issue.

## Acknowledgement

This report was produced by Barbara Albiger and Jane Knisely.

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**Annexes**

## Annex A: Abbreviations and acronyms

<b>AGISAR</b>	WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance
<b>AMR</b>	Antimicrobial resistance
<b>ANSE</b>	French Agency for Food, Environmental and Occupational Health & Safety
<b>ARHAI</b>	Antimicrobial Resistance and Healthcare-Associated Infections
<b>ARLG</b>	Clinical Research Network on Antibacterial Resistance
<b>CDC</b>	US Centers for Disease Control and Prevention
<b>CLSI</b>	Clinical Laboratory Standards Institute
<b>CMVP</b>	Committee for Medicinal Products for Veterinary Use
<b>DG RTD</b>	European Commission's Directorate-General for Research and Innovation
<b>DG SANCO</b>	European Commission's Directorate-General for Health and Consumers
<b>EC</b>	European Commission
<b>ECDC</b>	European Centre for Disease Prevention and Control
<b>ECOFFs</b>	Epidemiological cut-off values
<b>EEA</b>	European Economic Area
<b>EFSA</b>	European Food Safety Authority
<b>EMA</b>	European Medicines Agency
<b>ECCMID</b>	European Congress of Clinical Microbiology and Infectious Diseases
<b>ESCMID</b>	European Society of Clinical Microbiology and Infectious Diseases meeting
<b>ESVAC</b>	European Surveillance of Veterinary Antimicrobial Consumption
<b>EU</b>	European Union
<b>EUCAST</b>	European Committee on Antimicrobial Susceptibility Testing
<b>FDA</b>	US Food and Drug Administration
<b>GAIN</b>	Generating Antibiotic Incentives Now Act
<b>HAI</b>	Healthcare-associated infection
<b>HHS</b>	US Department of Health and Human Services
<b>ICAAC</b>	Interscience Conference on Antimicrobial Agents and Chemotherapy
<b>IMI</b>	Innovative Medicines Initiative
<b>LPAD</b>	Limited Population Antibacterial Drugs
<b>MDR</b>	Multidrug-resistant
<b>MRSA</b>	Methicillin-resistant <i>Staphylococcus aureus</i>
<b>NHSN</b>	National Healthcare Safety Network
<b>NIH/NIAID</b>	US National Institutes of Health / National Institute of Allergy and Infectious Diseases
<b>LTCFs</b>	European long-term care facilities

<b>OIE</b>	World Organisation for Animal Health
<b>PPS</b>	Point prevalence survey
<b>SOP</b>	Standard Operating Procedure
<b>TATFAR</b>	Transatlantic Taskforce on Antimicrobial Resistance
<b>ToR</b>	Term of References
<b>US</b>	United States of America
<b>WHO</b>	World Health Organization



## Annex B: TATFAR members

<b>TATFAR members</b>		
<b>United States delegation</b>		
HHS	US	Nils Daulaire
HHS	US	Anne Yu
CDC	US	Steve Solomon
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	Patrick McDermott
<b>European Union delegation</b>		
EC – DG SANCO	EU	John Ryan
EC – DG SANCO	EU	Paolo Guiglielmetti
EC – DG RTD	EU	Line Matthiessen
EMA	EU	David Mackay
EFSA	EU	Ernesto Liebana
ECDC	EU	Dominique L. Monnet
<b>EU Presidency trio representatives</b>		
Ireland	Eibhlín Connolly	
Lithuania	Loreta Asokliene	
Greece	Fofa Kaliva	

## Annex C: Scope and term of reference of TATFAR<sup>44</sup>

### *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 was a proposal with suggestions for areas of future collaboration between the EU and the US. The proposal was 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 AMR are well-documented and one more report describing the current situation and the risks posed by AMR 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 AMR. 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 Affairs (OGA)
- 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)

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<sup>44</sup> [Transatlantic Taskforce on Antimicrobial Resistance Report, 2011](#)

- 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 in order to keep the Council regularly informed of progress.

### *Focus areas*

The work of the taskforce was guided by the focus areas defined by the 2009 EU–US Summit declaration "to establish a transatlantic taskforce on urgent AMR 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."

### *TATFAR*

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 concluded its work by March 2011 and will continue beyond this timeframe after the consent of all parties.

### *Operating procedures*

The taskforce was co-chaired by the US and the EU. The chairs were appointed by consensus. The ECDC provided the taskforce with a secretariat to deal with the administrative aspects of organising and running the day-to-day arrangements until 31 December 2013.

The work was 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 held two face-to-face meetings. A kick-off meeting was held in the US in June 2010 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 second face-to-face meeting was held in the EU in March 2011 to provide orientation to the final recommendations.

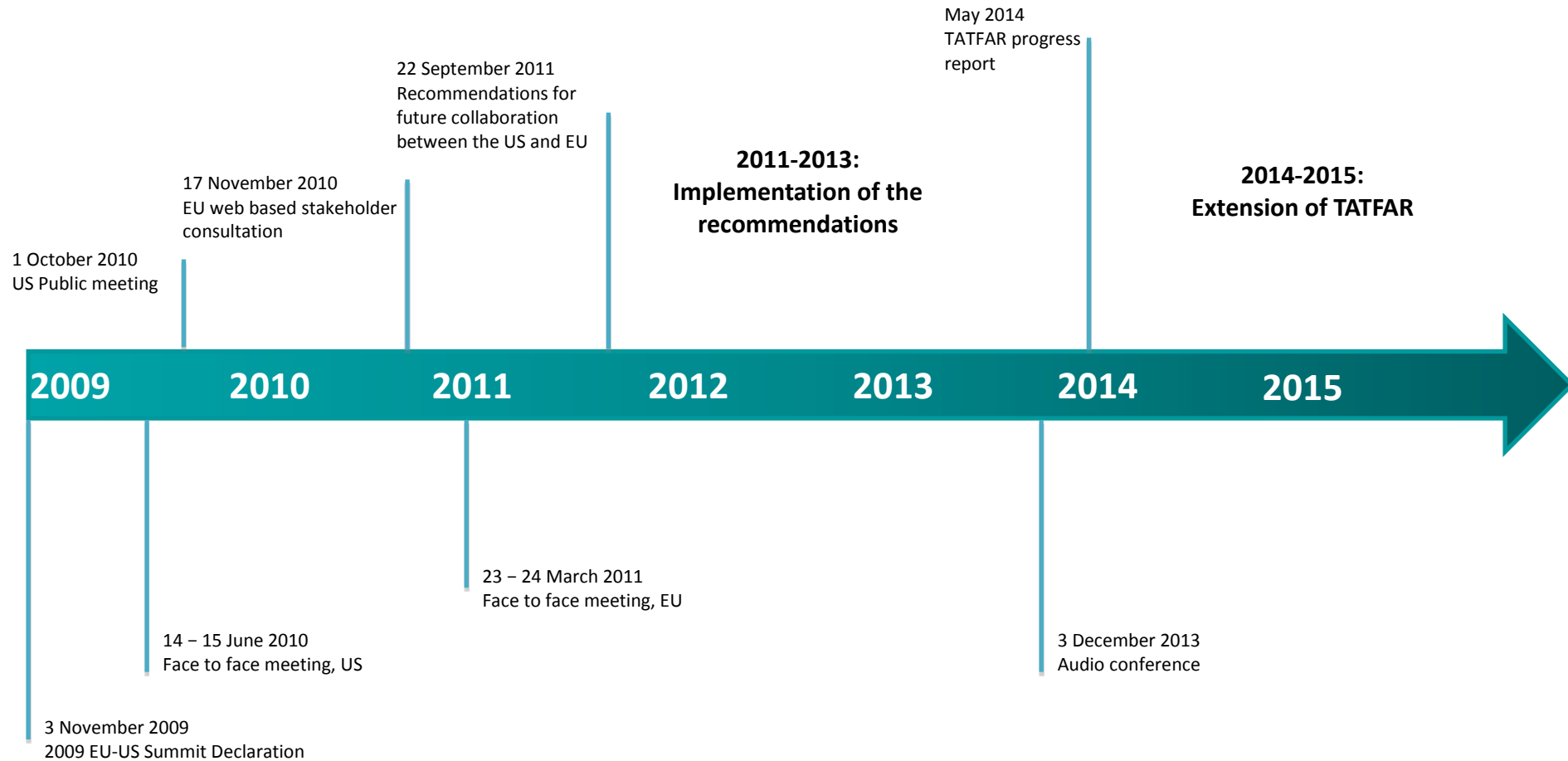
### *Consultation, external interaction, and workshops*

The US and EU partners of the taskforce sought, when 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: The TATFAR recommendations for future collaboration

TATFAR recommendations for future collaboration		
Key Area I. Appropriate therapeutic use in human and veterinary medicine		
Opportunity for collaboration	Recommendation	
Antimicrobial stewardship in human medicine	1	Develop common structure and process indicators for hospital antimicrobial stewardship programmes
Surveillance of antimicrobial use in human and veterinary communities	2	Convene a joint EU/US working group to propose standards for measuring antimicrobial use in hospital settings
	3	Collaborate in collection of data on sales and use of veterinary antimicrobial drugs in food-producing animals
Risk analysis on foodborne AMR		Collaborate on implementation of the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance prepared by Codex Alimentarius
	5	Enhance information sharing on approaches to promoting appropriate use in veterinary communities
	18	Establish a joint working group of international subject matter experts to identify key knowledge gaps in understanding the impact of antimicrobial use in animals on the risk to man from antimicrobial resistance
Campaigns to promote appropriate use in human medicine	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
Key Area II. Prevention of drug-resistant infections		
Surveillance of drug-resistant infections	7	Consultation and collaboration on a point-prevalence survey for HAIs
	8	Develop a process for transatlantic communication of critical events that may signify new resistance trends with global public health implications
	9	Encourage efforts to harmonise, to the extent possible, interpretive criteria for susceptibility reporting of bacterial isolates across surveillance programmes in the US and EU
Prevention strategies	10	Convene a workshop bringing together public health experts from the US and EU to develop consensus evaluation tools for hospital infection control programmes
	11	Develop a transatlantic strategy to facilitate vaccine development for HAIs
Key Area III. Strategies for improving the pipeline of new antimicrobial drugs		
Incentives to stimulate development of new antibacterial drugs in human medicine	12	Policymakers should strongly consider establishing significant incentives to stimulate antibacterial drug development
Research to support the development of new antibacterial drugs	13	Increase communication between US and EU research agencies to identify common scientific challenges that may represent opportunities for collaboration
	14	Publicise funding opportunities to EU, US research communities
Regulatory approaches for antibacterial products	15	FDA and EMA will discuss ways to facilitate the use of the same clinical development programme to satisfy regulatory submissions to both Agencies
	16	Establish regular meetings between FDA and EMA to discuss common issues in antibacterial drug development and regulation
	17	Exchange information on possible approaches to drug development for bacterial diseases where limited drugs are available

## Annex E: Timeline of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR), 2009-2013



## Annex F: 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 AMR. 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 US 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 2013 was to support efforts at national level to reduce unnecessary antibiotic use in hospitals and in the community through the development and dissemination of educational

materials promoting prudent antibiotic use. The motto for the European Antibiotic Awareness Day in 2013 is “Everyone is responsible.”

- [ABS \(AntiBiotic Strategies\) International](#) was a project to implement strategies for appropriate use of antibiotic drugs 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 target rational and cost-effective use of antibiotic drugs for the management of respiratory infections in primary care. Analyses of the cost-effectiveness of the different interventions that aim to improve antibiotic use have been performed. On the basis of 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 studies the impact of antibiotic exposure on antibiotic resistance with a multidisciplinary approach that bridges molecular, epidemiologic, clinical, and pharmacological research. Many results drawn from previous studies of the effect of antibiotic use on emergence, selection, and spread of AMR have lacked a holistic view. 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.
- In June 2013, ECDC published an evidence-based guidance for healthcare professionals presenting five key perioperative antibiotic prophylaxis modalities for preventing surgical site infections, based on systematic review<sup>45</sup>. The document includes evidence-based guidance, structure, and process indicators as well as implementation toolkits, when appropriate. ECDC

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<sup>45</sup> <http://ecdc.europa.eu/en/publications/Publications/Perioperative%20antibiotic%20prophylaxis%20-%20June%202013.pdf>



is also preparing systematic reviews and evidence-based guidance on organisation of hospitals antimicrobial stewardship programmes.

## 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 urinary tract infections, evaluating the epidemiology of in-patient antibiotic use, and 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 increase antibiotic resistance by promoting adherence to appropriate prescribing guidelines among providers, decreasing demand for antibiotic drugs for viral upper respiratory infections among healthy adults and parents of young children, and increasing adherence to prescribed antibiotic drugs 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](#) (HAPPY AUDIT) 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 antibiotic drugs. 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 worked 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](#)<sup>46</sup>.

## Product labelling and literature

### Joint activities

- The FDA and the 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

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<sup>46</sup> Hersh AL, Jackson MA, Hicks LA, American Academy of Pediatrics Committee on Infectious Diseases. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *Pediatrics*. 2013 Dec;132(6):1146-54.

- [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 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.  
In June 2013, the European Commission published [a report on the first five years of the regulation](#). The report concludes that paediatric development has become a more integral part of the overall development of medicinal products in the EU, with the Regulation working as a major catalyst to improve the situation for young patients. It also identifies some areas for improvement, such as the low uptake of the [paediatric-use marketing authorisation](#) (PUMA) by companies, which the Agency, together with the European Commission, intends to address during its fine-tuning of the current implementation of the regulation.

## US activities

- FDA has had [labelling regulations addressing the appropriate use of antibacterial drugs for use in humans](#) since 2003 (21 CFR Part 201.24). Antibacterial [labelling regulations addressing the proper use of antibiotics](#) since 2003 (21 CFR Part 201). Labelling for antibiotic drugs contains required statements that antibacterial drugs should be used only to treat patients with infections that are proven or strongly suspected to be caused by bacteria and also encourages healthcare professionals to counsel patients about proper use of antibacterial drugs.

## B. Surveillance of use of antibacterial agents in medical communities

### EU activities

- [The European Surveillance of Antimicrobial Consumption Network](#) (ESAC-Net), previously known as the European Surveillance of Antimicrobial Consumption project (ESAC), is a

Europe-wide network of national surveillance systems coordinated by ECDC that provides European reference data on antimicrobial drug use. All 28 EU Member States are reporting data on the use of drugs to treat infections caused by bacteria (antibacterial drugs), viruses (antivirals), and fungi (antimycotics).

- [ARPEC](#) (Antibiotic resistance and prescribing in European children) is a network that will develop a prospective surveillance system to monitor rates of prescribing antibiotic drugs and resistance in EU children. This surveillance will be used to determine the variation in choice of drug, dose, and indications for prescribing antibiotic drugs for common childhood infections in the community and hospitals between EU countries. ARPEC will propose a novel paediatric defined daily dose (DDD) method 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 hospitals, 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 antibiotic drugs in primary healthcare facilities. In nine European countries data are being collected on antibiotic drug resistance patterns of bacteria circulating in the community. This data will be compared with antibiotic drug 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.
- In 2011–2012, ECDC conducted the first EU-wide point prevalence survey (PPS) of HAIs and antimicrobial drug use in acute care hospitals in 30 EU/EEA Member States. An estimated 2800 healthcare workers from 1200 hospitals across Europe were trained by national PPS coordinating staff to implement the standardised PPS methodology. Data from a total of 273

753 patients in 1149 hospitals were submitted to ECDC in order to estimate the prevalence of healthcare-associated infections in European hospitals.

- [HALT-2](#) (Healthcare-associated infections in long-term care facilities) is a project funded by ECDC to extend the control of healthcare-associated infections and AMR in European long-term care facilities (LTCFs) by performing repeated point prevalence surveys on healthcare-associated infections, AMR, antibiotic use, current infection control, and antimicrobial stewardship practices and resources in all 28 EU Member States, 3 EEA/EFTA, and 2 EU enlargement countries. This project builds on the results of a previous ECDC-funded project (2009-2011) that aimed to develop and implement a protocol for surveillance of HAI, antimicrobial use, and resistance in European LTCFs in order to establish baseline rates and identify priorities for improvement.

## 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 US, including acute care hospitals, long-term acute care hospitals, psychiatric hospitals, rehabilitation hospitals, outpatient dialysis centres, ambulatory surgery centres, and long-term care facilities. In 2011, CDC launched a new version of the Antibiotic Use Module of the NHSN that permits electronic reporting of antimicrobial drug use data from healthcare facilities.
- 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 US. Findings are based on a sample of visits to non-federal, 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 use data that may allow for comparisons in antimicrobial use rates and trends between countries.
- CDC and the 10-state Emerging Infections Program (EIP) launched a healthcare-associated infection and antimicrobial use [point prevalence survey](#) in 2011 that was conducted in general, acute-care hospitals in the 10 EIP states. The 2011 survey yielded 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

### EU activities

- Prior to conducting the EU-wide PPS of HAIs and antimicrobial use in acute care hospitals<sup>47</sup>, ECDC developed a standardised methodology, training materials, a “train-the-trainer” course for national PPS coordinating staff, free hospital software for data collection, and a validation methodology. The ECDC PPS and the national PPS coordinating team trained approximately 2800 hospital staff.

### US activities

- CDC supported the development of web-based medical school curriculum on appropriate antibiotic drug use on the basis of curriculum that has been pilot tested at several medical schools. The curriculum was launched online in 2013. The curriculum is intended for third- and fourth-year medical students.
- CDC's Get Smart: Know When Antibiotics Work programme developed a continuing education programme and new web content to train community pharmacists to incorporate appropriate antibiotic use education into practice. Educational materials and guidelines for healthcare providers are 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

### Joint activities

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<sup>47</sup> <http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf>

- In 2013, ECDC and CDC, with partner agencies in Canada and Australia published a joint editorial entitled “Global collaboration essential to spread the message on prudent antibiotic use”<sup>48</sup> on prudent antibiotic use campaigns in the US and EU, as well as in Canada and Australia in *Lancet Infectious Diseases*.

## EU activities

- Full issue of [Eurosurveillance](#) dedicated to the topic of AMR was published in coordination with European Antibiotic Awareness Day 2010 with articles from ECDC, France, the Netherlands, and multinational groups.
- ECDC funded the development of a pilot [e-learning module](#) for continuous medical education on use of antibiotic drugs 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 antibiotic drugs but also teaches prudent antibiotic use and how inappropriate use can have an adverse effect on a person's good microbes and antibiotic drug resistance in the community. The project is led by the Public Health England (PHE) Primary Care Unit in UK, and involves a consortium of 24 partner EU/EAA countries and 3 non-EU countries. Project development was 60% funded by DG SANCO. Since 2010, the website has been supported by PHE in England. ECDC supported translation of all the resources into the other European languages.
- ECDC developed a toolkit of template materials for national health authorities to adapt and use as part of national campaigns on appropriate antibiotic drug use for hospital prescribers. Endeavours to help intervention planners 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 the toolkit components. This formative

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<sup>48</sup> [http://ac.els-cdn.com/S1473309913703153/1-s2.0-S1473309913703153-main.pdf?\\_tid=796472d0-5775-11e3-b8bc-00000aab0f6b&acdnat=1385564961\\_50cf2afa2d52761d1b6ee170d3bdfd6f](http://ac.els-cdn.com/S1473309913703153/1-s2.0-S1473309913703153-main.pdf?_tid=796472d0-5775-11e3-b8bc-00000aab0f6b&acdnat=1385564961_50cf2afa2d52761d1b6ee170d3bdfd6f)

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 in which 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 the following initiatives:

The Communication of 15 November 2011 from the Commission to the European Parliament and the Council - Action Plan against the rising threats from Antimicrobial Resistance. The European Commission proposes to put in place a five-year action plan to fight against AMR based on 12 key actions<sup>49</sup>. The Commission has published a road map on the implementation of the 5 years action plan<sup>50</sup> and convened a conference in December 2013 as part of a mid-term review of the implementation of the Action Plan.

The [Council of the European Union](#) has adopted several conclusions related to AMR and use of antimicrobial drugs in veterinary medicine. For example, the Council conclusions of 22

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<sup>49</sup> [http://ec.europa.eu/health/antimicrobial\\_resistance/policy/index\\_en.htm](http://ec.europa.eu/health/antimicrobial_resistance/policy/index_en.htm)

<sup>50</sup> [http://ec.europa.eu/health/antimicrobial\\_resistance/policy/index\\_en.htm](http://ec.europa.eu/health/antimicrobial_resistance/policy/index_en.htm)



June 2012 on the impact of AMR in the human health sector and in the veterinary sector – a "One Health" perspective<sup>51</sup>.

During its plenary sitting of 11 December 2012, the European Parliament adopted a Report on the Microbial Challenge – Rising threats from Antimicrobial Resistance (2012/2041 (INI)) – adopted 11 December 2012<sup>52</sup>.

The European Parliament adopted a resolution on antibiotic resistance on 12 May 2011 and a resolution on the public health threat of AMR on 27 October 2011.

Also the following provisions and legislative proposals are in place

- Marketing authorisation requirements, antimicrobial drugs prescription-only medicines (Veterinary Medicines Directive 2001/82/EC);
- New legislation on monitoring and reporting of AMR in *Salmonella*, *Campylobacter*, and indicator commensal *E. coli* and *Enterococcus* spp. Commission Implementing Decision 2013/652/EU on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria<sup>53 54</sup>;
- Ban on the use antimicrobial drugs for *Salmonella* eradication in poultry (Commission Regulation 1177/2006).

- Research related to animal health, biosecurity on farms, vaccines, bacteriophages, breeding of more robust or disease resistant animals, substitutes to antimicrobial growth promoters.
- As an example, the following activities have been undertaken by different EU Member States:
  - Animal healthcare programmes/agreement systems. They aim to improve veterinary-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 antimicrobial drugs
  - Specific requirements for pre-treatment susceptibility testing for group treatments
  - Strategic programmes involving human and veterinary medicine, joint AMR surveillance

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<sup>51</sup> Reference: OJ C 211, 18.7.2012, p.2

<sup>52</sup> Reference: OJ C 77E, 15.3.2013, p. 20

<sup>53</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:303:0026:0039:EN:PDF>

<sup>54</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:303:0026:0039:EN:PDF>

- 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 for animals<sup>55</sup>, and third- and forth-generation cephalosporins<sup>56</sup>, macrolides<sup>57</sup>, colistin<sup>58</sup>, glycylicyclines,<sup>59</sup> and pleuromutilins<sup>60</sup>.

## 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 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 AMR. It is co-chaired by FDA, CDC, and 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 AMR issues.
- The One Health approach to the health and well-being of all species has been endorsed by the US agencies participating in TATFAR and offers many promising avenues of collaboration between the US and the EU<sup>61 62</sup>.

<sup>55</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Public\\_statement/2009/10/WC500005152.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/10/WC500005152.pdf)

<sup>56</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/10/WC500004307.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004307.pdf)

<sup>57</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2010/11/WC500099151.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099151.pdf)

<sup>58</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/07/WC500146813.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146813.pdf)

<sup>59</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/07/WC500146814.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146814.pdf)

<sup>60</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/11/WC500154734.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500154734.pdf)

<sup>61</sup> <http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm109489.htm>

<sup>62</sup> <http://www.cdc.gov/onehealth/>

- [NARMS](#), established in 1996, continually monitors AMR 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 for AMR 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 Member States, certain antimicrobial drugs (e.g. fluoroquinolones) cannot be used unless a recent diagnostic test reveals that no other antimicrobial drug is effective for that disease in that specific herd. Appropriate diagnostic testing is controlled and compared to the treatment guidelines. In some Member States, microbiologic 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 AMR.

## EU activities

- [European Medicines Agency's](#) Committee for Veterinary Medicinal Products (CVMP) has guidelines on the Summary of Product Characteristics (SPC) for antimicrobial products, which takes into account how AMR has developed in recent years and provides detailed guidance on responsible use of antimicrobial drugs.
- CVMP has developed [reflection papers](#) on the use of fluoroquinolones, third- and fourth-generation cephalosporins, macrolides, pleuromutilins, and colistin in food producing animals. These papers contain recommendations regarding prudent use to be included in the summary of product characteristics (SPCs) for such products. The CVMP has been using referrals as a legal tool to implement prudent use warnings on the SPC of some antimicrobial drugs (e.g., (fluoro) quinolones or third- and fourth-generation cephalosporins).
- A draft guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances is currently under consultation. The guideline provides recommendations for the design and conduct of pre-clinical and clinical studies to support clinical efficacy for an antimicrobial veterinary medicinal product.

## 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 pre-approval mechanism to evaluate the safety of antimicrobial animal drugs with regard to their microbiologic effects on bacteria of human health concern. Guidelines lay out a qualitative risk assessment approach to new animal antimicrobial drugs and apply risk management strategies to minimise any impact on human health.
- FDA has produced several quantitative risk assessments on the issue of antimicrobial resistant bacteria in animals because of the use of antimicrobial drugs in animals transferring

to humans and causing antimicrobial-resistant infections, e.g., fluoroquinolone-resistant *Campylobacter* in poultry, macrolide resistance, and others. For qualitative risk assessments, see Guidance for Industry #152, above.

- FDA [Guidance for Industry #209](#), The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals, published 13 April 2012, 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 ensuring that medically important antimicrobial drugs are used judiciously in food-producing animals in order to help minimise AMR 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 routinely in poultry and can only be used as an exception and “off-label” under the control a prescribing veterinary surgeon. Such use, therefore, does not cover routine in ovo injection or treatment of 1-day-old chicks. EMA has reinforced that cephalosporins should not be used in poultry, including in all SPCs for third- and fourth-generation cephalosporins a specific prohibition of off-label use, using the phrase “Do not use in poultry.” The specific recommendations on these classes of cephalosporins can be found as part of the report on the referral from the European Commission to the EMA under Article 35 of [Directive 2001/82/EC](#), which encompassed all veterinary medicinal products containing systemically administered (parenteral and oral) third- and fourth-generation cephalosporins intended for use in food-producing species.
- Regarding AMR linked to the use of antimicrobial agents in companion animals, the CVMP has published a reflection paper on the risk of AMR transfer from companion animals<sup>63</sup>. Although this document does not directly address the off-label use in companion animals this subject is currently under discussion and is likely to be the subject of a reflection paper. In addition, EMA has received a request from the European Commission for advice on what the possible impact could be on the treatment of resistant bacteria in humans of granting marketing authorisations for new classes of veterinary antibiotic drugs, and whether the use of certain new classes of antimicrobial drugs or antibiotic substances (especially those that are important in human medicine) that are currently not authorized needs to be restricted in

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<sup>63</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/10/WC500152665.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/10/WC500152665.pdf)

animals. When answering this request, the EMA will take into account the off-label use of antibiotic drugs in animals.

- In some EU Member States, there are restrictions or bans on off-label use and restrictions on the use of certain antimicrobial drugs that are critical for use in humans for all animal species.

### **US activities**

- The FDA [prohibits the extra-label use](#) of certain antimicrobial drugs in food-producing animals because of 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 antimicrobial drugs are prescription-only medicines.

### **US activities**

- FDA issued the 2012 final [Guidance to Industry #209](#) announcing 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).
- In 2013 FDA issued final [Guidance for Industry #213](#), which began the three-year timeframe to implement the plan announced in 2012.

## **B. Surveillance of use 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 AMR in animals. In October 2013, the Agency published its third report on sales of veterinary antimicrobial drugs from the ESVAC project<sup>64</sup>. A total of 25 EU and EEA countries submitted data on 2011 sales to the Agency. The 2013 report, as well as the reports from 2012 and 2011, will be used by risk assessors and risk managers in the European Commission and Member States to inform antimicrobial policy and the responsible use of antimicrobial drugs.
- The ESVAC project has recently revised its reflection paper on collecting data on the use of antimicrobial agents by animal species<sup>65</sup>, on technical units of measurement, and indicators for reporting use of antimicrobial agents in animals. This document discusses how to establish systems for collecting reliable and standardised data on the use of antimicrobial agents by animal species for the ESVAC database and how to report the data taking into account the differences in dosing between the various antimicrobial agents as well as the animal population at risk for treatment.
- Member States provide the necessary data on the use of antimicrobial drugs and on AMR in humans, animals, and food in the EU. A common analysis by the three agencies, EFSA, EMA, and ECDC, of these data, with joint conclusions on the occurrence of AMR in humans, animals, and food should result in a joint report of the three agencies, with harmonised and transparent presentation of the data. The first ECDC/EFSA/EMA joint report on the analysis of the relationship between the use of antimicrobial agents and occurrence of AMR in the human and animal sector will be produced in 2014.

## US activities

- FDA is implementing Section 105 of the Animal Drug User Fee Amendments of 2008 to collect and publish animal [antimicrobial drug distribution data](#).
- In 2012, [FDA solicited broad public comment](#) on enhancements to the existing requirements related to the reporting of antimicrobial drug sales/distribution data, as well as input on alternative methods for monitoring antimicrobial use in food-producing animals.

<sup>64</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/10/WC500152311.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500152311.pdf)

<sup>65</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/10/WC500152665.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/10/WC500152665.pdf)

- In September 2013 [FDA sought additional public input](#) on a new proposed format for the annual summary and expects to use the enhanced format when it summarizes the data reported for 2012.

## C. Promotion of training of health professionals in veterinary communities

### EU activities

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

### US activities

- FDA awarded a contract to develop a web-based decision support system to be used by veterinarians to select and use antimicrobial agents appropriately. The Veterinary Antimicrobial Decision Support ([VADS](#)) System continues to be revised and improved.
- FDA produced a nine-minute [animation](#) explaining to veterinarians how AMR both emerges and proliferates among bacteria.
- FDA produced several [videos](#) and accompanying booklets on the prudent use of antimicrobial drugs.
- 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 antimicrobial drugs at national level also for veterinary medicine.
- [EPRUMA](#) is a multi-stakeholder platform that links 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 the judicious use of antimicrobial drugs that was targeted to food animal producers. These materials 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

- Point prevalence surveys of antimicrobial use and HAIs. Since 2009, CDC and ECDC worked together in attempts to harmonise key methods related to both ECDC and US PPS. Furthermore, in the planning phase of a pilot prevalence survey of HAIs and antimicrobial use in nursing homes, CDC is currently working with EU investigators to use a similar methodology for the US survey as that used for the ECDC-funded Healthcare-Associated Infections in Long-Term Care Facilities (HALT) project.

## 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 AMR for public health. It is coordinated by ECDC.

- [The European Surveillance of Antimicrobial Consumption Network](#) (ESAC-Net), previously known as formerly the European Surveillance of Antimicrobial Consumption project (ESAC), is a Europe-wide network of national surveillance systems, providing European reference data on antimicrobial drug use. 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 Hospitals in Europe Link for Infection Control through Surveillance and Improving Patient Safety in Europe.
- [DebugIT](#) (Detecting and Eliminating Bacteria Using Information Technology) is a project financed by the Directorate-General Information Society of the European Commission. It will use clinical and operational information from clinical information systems 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 to provide the scientific basis for an early warning system when isolates of a particular epidemicity appear in the community and in hospitals.
- For the veterinarian sector, EFSA is performing the surveillance of antimicrobial surveillance. EFSA recently published several scientific reports with recommendations on harmonised monitoring, analysis, and reporting of data:
  - Technical specifications on harmonised monitoring and reporting of AMR in *Salmonella*, *Campylobacter*, and indicator *E. coli* and *Enterococci* bacteria transmitted through food (June 2012)<sup>66</sup>
  - Technical specifications on harmonised monitoring and reporting of AMR in MRSA in food-producing animals and food (October 2012)<sup>67</sup>

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<sup>66</sup> <http://www.efsa.europa.eu/en/efsajournal/doc/2742.pdf>

<sup>67</sup> <http://www.efsa.europa.eu/en/efsajournal/doc/2897.pdf>

- Technical specifications for the analysis and reporting of data on AMR in the EU Summary Report (February 2012)<sup>68</sup>
  - The EU Summary Report on AMR in zoonotic and indicator bacteria from humans, animals and food in 2011 (2013)<sup>69</sup>.
- Upon a request from DG SANCO to review and harmonised the surveillance systems on AMR in the EU, EFSA published a scientific report that revised the existing technical specifications on the monitoring and reporting of AMR in the food chain. This report, as well as other scientific opinions of EFSA, is the basis of the newly reviewed EU legislation on AMR in the food chain. The new legislation ([Decision 2013/652/EU](#)) lays down the requirements for the harmonised monitoring of the most relevant, from a public health perspective, combinations of bacterial species/food producing animal populations/food and includes detailed rules for sampling, analysis of the isolates, and interpretations of the results. The legislation also includes the requirements for the harmonised monitoring and reporting of ESBL-, AmpC, and carbapenemase-producing bacteria in certain animal populations and in certain food types<sup>70</sup>.

## 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 aimed 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 EIP sites around the US.
- Healthcare Associated Infections-Community Interface ([HAIC](#)) projects within the EIP: 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 performed the 2011 acute care hospital HAI and antimicrobial use prevalence survey and performed time-limited projects evaluating innovations in HAI surveillance methods.

<sup>68</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/2587.htm>

<sup>69</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/3196.htm>

<sup>70</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:303:0026:0039:EN:PDF>

- [Surveillance for healthcare-associated infections using NHSN](#): For a description of NHSN, see I.1.b.7. CDC measures HAIs and AMR associated with these infections in NHSN. In aggregate, CDC analyses and publishes surveillance data to estimate and characterise the national burden of HAIs. 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.
- CLSI, in collaboration with EUCAST, held a workshop on 12 January 2013 CLSI to discuss the science of setting ECOFFs. Scientific principles outlined in this workshop will serve as a foundation for establishing harmonized ECOFFs in the future.

## B. Ongoing Activities – Prevention

### EU activities

- [ABS \(AntiBiotic Strategies\) International](#) was a project to implement strategies for appropriate use of antibiotic drugs in hospitals in EU Member States. It was funded 2006–2008 and was a partnership of nine EU Member States: 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.
- In June 2013, ECDC published an evidence-based guidance for healthcare professionals presenting five key perioperative antibiotic prophylaxis modalities for preventing surgical site infections on the basis of systematic review<sup>71</sup>. The document includes evidence-based guidance, structure and process indicators, as well as implementation toolkits, when appropriate. ECDC systematic review and evidence-based guidance on organisation of hospital infection control programmes is expected to be published in December 2014.
- [IMPLEMENT](#) (Implementing strategic bundles for infection prevention and management) is a project that aims to identify current national and local implementation strategies for preventing and managing 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.

<sup>71</sup><http://ecdc.europa.eu/en/publications/Publications/Perioperative%20antibiotic%20prophylaxis%20-%20June%202013.pdf>

- [PROHIBIT](#) (Prevention of hospital infections by intervention and training) is a project 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.
- [Carbapenem resistance in food animal ecosystems](#): EFSA reviewed the information on the epidemiology of acquired resistance to carbapenems, including the genes coding for such resistance, in food-producing animals and food and identified possible means of preventing or minimising the further emergence and spread of carbapenemase-producing bacterial strains transmitted via the food chain, including consideration of the advantages and disadvantages of different options. Recommendations are given on how to prevent the emergence of resistant bacteria<sup>72</sup>.

## 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 the public health response. Several states are currently assessing local epidemiology and prevention practices used by the healthcare delivery sector.
- American Recovery and Reinvestment Act (ARRA): Funded state MRSA, *C. difficile*, and other multidrug-resistant organisms (MDRO) prevention collaborative programs that use 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 HAIs, antibiotic resistance, and other adverse events associated with healthcare. These Epicenters study topics such as MRSA, vancomycin-resistant

<sup>72</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/3501.htm>

enterococci, 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 HAIs in US healthcare facilities. One of the primary functions of the committee is to issue recommendations for preventing and controlling HAIs in the form of guidelines, resolutions, and informal communications.
- A statewide collaborative to prevent infections caused by 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 multistate 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 is intended for 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 more than 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 and developed a core curriculum for this purpose. After assessing the training needs for infection control in Europe, ECDC proposes a strategy for basic training at the EU level in the area of infection control. In June 2013, ECDC published the core competencies for infection control and hospital hygiene professionals in the European Union<sup>73</sup>. TRICE recommended adoption and endorsement of the European Infection Control and Hospital Hygiene (IC/HH) Core Competencies. TRICE-IS is a ECDC-funded project building on the results of the TRICE project with the aim to implement a strategy to support the national/regional infection control/hospital hygiene training programmes in EU Member States, EEA/EFTA countries, and EU acceding countries.

## 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 collaborative programs 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 HAIs. 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 *S. 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

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<sup>73</sup> <http://ecdc.europa.eu/en/publications/publications/infection-control-core-competencies.pdf>

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

## 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.

## E. Ongoing research activities – Vaccines

### US activities (NIH/NIAID)

- CDC established three active research collaborations with vaccine developers for *C. difficile* infections to collect data and define the risks.
- The National Institutes of Health (NIH), in collaboration with CDC and FDA, convened a workshop on how to overcome the challenges in *S. aureus* vaccine development with the objectives to discuss the lessons learned from recent Staph vaccine clinical trials, address the challenges in developing a Staph vaccine (basic, translational, and clinical research limitations) and potential ways to overcome them, and identify novel scientific approaches to Staph vaccine development  
(<https://respond.niaid.nih.gov/conferences/staphvaccineworkshop2013/Pages/default.aspx>) on 7 June 2013 (Rockville, MD).

### EU activities (European Commission/DG RTD)

Following a call published by DG RTD (HEALTH.2013.2.3.1-1: Drugs and vaccines for infections that have developed or are at the risk of developing significant antimicrobial resistance) within the [7<sup>th</sup> Framework programme](#), several projects support the research and development of vaccines for bacterial infections have been funded.

- [NeoStrep](#) (Development of Group B Streptococcal vaccine to alleviate emerging antibiotic resistance through elimination of current prophylactic antibiotic strategies in GBS prevention) will develop a novel vaccine against Group *B Streptococcal* (GBS) infections, responsible for 50% of life-threatening infections in newborn babies. The goal is to provide a safe and effective alternative to current generally implemented antibiotic prophylaxis.



- [BELLEROPHON](#) (comBinig cELLular and humoral immunE RespOnses as a vaccine strategy against staPHhyLOcoccus aureus pathogeN) will design, manufacture, and assess in a Phase I clinical study a novel *S. aureus* vaccine candidate targeting both the cellular and humoral responses. It is designed to be protective against both MRSA and more sensitive *S. aureus* strains.
- [CD-VAX](#) (Oral Vaccination against *Clostridium difficile* Infection) will use a novel mucosal vaccine delivery system based on the use of inactivated *Bacillus subtilis* spores that express two different recombinant *C. difficile* antigens on their surface, a toxoid antigen, and a unique spore colonisation factor. The project will address its safety and immunogenicity in both preclinical and phase I clinical studies.

### 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/NIAID funding. A complete list of funded AMRs grants can be found at the [NIH RePORT website](#). Examples of AMR 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, scientists have sequenced the genomes of

more than 6500 bacterial strains, including 550 *S. aureus*, 425 *Enterococcus* species, 150 *Streptococcus pneumoniae*, and 265 *Acinetobacter* species. In addition, NIH/NIAID has initiated new genome sequencing studies of important antibiotic resistant bacterial pathogens, including sequencing the genomes of more than 500 CRE isolates. NIH/NIAID supports Bioinformatics Resource Centers that serve to 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 freely 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 and lower the financial risks incurred by industry to develop novel antimicrobial drugs. These services are freely available to the international research community. More information can be found [here](#).
- 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 Fiscal Year (FY) 2012, NIAID awarded 12 phased innovation partnership awards under the "Targeting Resistance in Select Gram-Negative Pathogens" research initiative ([RFA AI-11-009](#)). 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. Interested parties are encouraged to subscribe to [NIAID's funding newsletter](#) to stay abreast of upcoming funding opportunities.

### Clinical research

- 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. Each of these support mechanisms is available to the international research community. More information on funded NIAID clinical trials with relevance to AMR can be found [here](#).

- NIAID is supporting clinical trials to inform the rational use of existing antimicrobial drugs to help limit the development of AMR. Since 2007, NIAID has made multiple 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. These trials are ongoing or in development. More information about the trials 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 and acute otitis media and community-acquired pneumonia ([2010](#)).
- In June 2013, NIH/NIAID launched the Leadership Group for a Clinical Research Network on Antibacterial Resistance (ARLG), a major new clinical effort to address AMR. The ARLG has developed a [clinical research agenda](#) identifying the most important clinical questions in antibacterial resistance. Studies conducted by the ARLG may include clinical testing of new drugs to treat MDR gram-negative bacteria, evaluating diagnostic devices in clinical settings, evaluating the effectiveness of new antimicrobial stewardship programs, and optimizing treatment regimens to reduce the emergence of resistance

### **EU activities (European Commission/DG RTD)**

- The European Commission (DG RTD) issued annual calls under the Seventh Framework Programme. In this programme, which runs from 2007 through 2013, antimicrobial drug resistance constitutes one of four areas in infectious diseases research. The other three areas target specific pathogens or groups of pathogens (the three poverty-related HIV, malaria, tuberculosis, the emerging [viral] epidemics and the neglected [tropical] infectious diseases). MDR-HIV and MDR-tuberculosis are exclusively considered under the area “HIV/AIDS, malaria and tuberculosis.” Although viral, fungal, and parasitic drug resistance are not excluded in “antimicrobial drug resistance,” most of the resistance problems are found in bacteria, which therefore constitute the bulk of the projects funded.

Collaborative research projects funded under the EU Seventh Framework Programme for Research (FP7) address different topics related to AMR. Each project 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 programme 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 through this programme 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 resistance and reduce the spread of resistant microbes.
- Developing novel antimicrobial therapies – Research projects in this area focus on new use of existing antibiotic drugs, the development of new antibiotic drugs, 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 antibiotic drugs should be prescribed and which antibiotic drugs 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.

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

The work programme for 2011 featured several call topics in the area of AMR, which in that call was a priority area. Proposals were required to address research needs described in the following five call topics

- Investigator-driven clinical trials of off-patent antibiotic drugs
- Multidisciplinary research on the evolution and transfer of antibiotic resistance
- Management of gram-negative multidrug-resistant infections
- Development of multi-analytic diagnostic tests
- Development of tools to control microbial biofilms with relevance to clinical drug resistance

For the above listed call topics, [10 research projects](#) have been funded.

The work programme for 2012 featured a call topic on diagnostics for infectious diseases. This led to the funding of two projects that will develop diagnostic tools to detect bacteria and resistance markers.

AMR featured as a priority area in the work programme for 2013, which included a novel initiative to unlock the potential of small and medium-sized enterprises. Proposals were required to address research needs described in the following five call topics:

- Development of drugs, vaccines, or novel therapies
- Stratified approaches to antibacterial/antifungal treatment
- Ecology and transfer of AMR throughout the food chain
- Nanotherapeutics to treat bacterial infectious diseases

For the above listed call topics, 15 research projects have been funded. More information on the funded projects can be found [here](#).

In March 2012, the [Innovative Medicines Initiative](#) (IMI) launched its first call for proposals under the "New Drugs for Bad Bugs" (ND4BB) programme, a major public-private partnership effort to address bottlenecks in discovery and development of new antibiotic drugs. Seven ND4BB projects with a total committed budget of more than €600 million have since either started or are in preparatory phases. They have five principal aims: 1) to create a sustainable EU clinical investigator and laboratory network with the capacity to run large-scale antibiotic clinical trials; 2) to use that network for improved and more efficient clinical development of new antibiotic drug candidates; 3) to advance our understanding of the underlying science, notably penetration barriers, and efflux mechanisms in gram-negative bacteria; 4) to progress promising novel hit or lead molecules into early clinical development; and 5) to develop options for novel economic models of antibiotic research and development and responsible use of antibiotic drugs.

EU Member States are coordinating their activities and pooling their national research in order to increase the effectiveness and impact of European public efforts. On this basis, a [Joint Programming Initiative](#) (JPI) entitled "The Microbial Challenge - An Emerging Threat to Human Health" has been set up. The initiative involves 17 European countries plus Israel, and was recently joined by Canada and could be a good starting point for engaging in a global initiative. A first joint call with Canada was announced on 15 November, and the strategic research agenda of this JPI will be launched on 3 April 2014.

The EU Seventh Framework Programme for Research ends in 2013, but research to combat AMR will also be supported in the new programme, [Horizon 2020](#) (2014-2020). The first work programme for Horizon 2020 was launched on 11 December 2013, and this includes a topic to

support identification and control of new and emerging infectious diseases including those from antimicrobial/resistant pathogens<sup>74</sup>.

## B. Ongoing regulatory activities

### Joint activities

- International Conference on Harmonisation (ICH): Through the ICH, the EMA and the US FDA have developed a number of guidance documents on preclinical and clinical development of drugs. The available guidance documents<sup>75</sup> include the following:
  - E8 General Considerations for Clinical Trials<sup>76</sup>
  - E9 Statistical Principles for Clinical Trials<sup>77</sup>
  - E10 Choice of Control Group and Related Issues in Clinical Trials<sup>78</sup>
  - E11 Clinical Investigation of Medicinal Products in the Pediatric Population<sup>79</sup>
  - E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs<sup>80</sup>
  - ICH M3(R2), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals<sup>81</sup>

Of note is that the guidance documents listed above were developed by the ICH process – guidance documents that both the EMA and the US FDA rely on. In addition to these, there are also guidance documents on a wide range of other topics about 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)

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<sup>74</sup> <http://ec.europa.eu/programmes/horizon2020/en/area/health>

<sup>75</sup> Guidance Documents can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

<sup>76</sup> The Guidance Document *E8 General Considerations for Clinical Trials* is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073132.pdf>

<sup>77</sup> The Guidance Document *E9 Statistical Principles for Clinical Trials* is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf>

<sup>78</sup> 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>

<sup>79</sup> 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>

<sup>80</sup> 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>

<sup>81</sup> 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>

## Recent and current activities in the area of antibacterial drug development

- The FDA has participated in a number of meetings held by public-private partnerships to address a number of important topics to facilitate the development of new antibacterial drugs. EMA, NIH/NIAID, and CDC have also participated in a number of these meetings. The meetings held by the Brookings Institution: Engelberg Center for Health Care Reform, the Foundations for the National Institutes of Health Biomarkers Consortium, and the Clinical Trials Transformation Initiative are listed below.
  - Brookings Institution: Engelberg Center for Health Care Reform - The Brookings Council on Antibacterial Drug Development has a goal to identify steps to address the major technical, regulatory, and financial barriers impeding antibacterial drug development. Meetings of the Council have included
    - Facilitating Antibacterial Drug Development; 9 May, 2012
    - Brookings Council on Antibacterial Drug Development Kick-Off Meeting; 30 August, 2012
    - Incentives for Change: Addressing the Challenges in Antibacterial Drug Development; 27 February, 2013
    - Special Medical Use: Limited Use for Drugs Developed in an Expedited Manner to Meet an Unmet Medical Need; 1 August, 2013
- Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium - The FNIH Biomarkers Consortium embarked on a project to identify clinical efficacy endpoints for clinical trials of Acute Bacterial Skin and Skin Structure Infections (ABSSSI), Community-Acquired Bacterial Pneumonia (CABP), and HABP/VABP. Meetings and accomplishments of the project team include the following:
  - First meeting of the project team for ABSSSI/CABP endpoints: focus on ABSSSI; 20 May, 2010
  - Follow-up meeting of the project team for ABSSSI/CABP endpoints: focus on CABP; 2 June, 2010
  - Discussion of endpoint development for additional indications, and preliminary results of the retrospective reviews of completed trials; 26 & 27 January, 2011
  - Discussion of interim efficacy endpoint recommendations for ABSSSI and CABP based on results of the retrospective reviews of completed trials; 8 July, 2011
  - Recommendations to FDA for interim efficacy endpoints ABSSSI and CABP with the submission of comments to the docket for the draft guidance

documents ABSSSI and CABP; 26 August, 2011 and publication of "Progress on Developing Endpoints for Registrational Clinical Trials of Community-Acquired Bacterial Pneumonia and Acute Bacterial Skin and Skin Structure Infections: Update From the Biomarkers Consortium of the Foundation for the National Institutes of Health" by George H. Talbot, John H. Powers, Thomas R. Fleming, Judith A. Siuciak, John Bradley, Helen Boucher, and on behalf of the CABP-ABSSSI Project Team in *Clin Infect Dis.* (2012) 55 (8): 1114-1121 first published online 28 June, 2012.

- First meeting of the project team for HABP/VABP endpoints; 24 April, 2013

– Clinical Trials Transformation Initiative – The Accelerating Antibacterial Drug Development project has a goal of identifying challenges, exploring novel solutions, and issuing recommendations on speeding up the development of new antibacterial drugs. Meetings of the CTTI group include the following:

- CTTI Think Tank on Unmet Medical Need and Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP); 11 & 12 October, 2012
- Quality by Design in HABP/VABP trials; 22 & 23 April, 2013
- Quality by Design in HABP/VABP trials; 29 August, 2013 (via teleconference):
- Safety data collection in HABP/VABP trials; 12 November, 2013

– The FDA has been updating its guidance documents to describe recommended clinical trial designs for studying antibacterial drugs. In some circumstances, the FDA has held public workshops to discuss the science or FDA Advisory Committee meetings and 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.

- FDA Advisory Committee Meetings Focusing on clinical trial designs
  - Community Acquired Bacterial Pneumonia; November 2011
  - Hospital Acquired Bacterial Pneumonia / Ventilator-Associated Bacterial Pneumonia; November 2011
  - Community Acquired Pneumonia April 2008; December 2009
  - Acute Bacterial Skin and Skin Structure Infections; November 2008
- 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 AMR; 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
- There have also been FDA Advisory Committee discussions on clinical trial design in the context of specific antibacterial drug products that informed recommendations on clinical trial designs. These efforts to date have resulted in publication of updated guidance documents on developing antibacterial drugs 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: Final November 2010
  - Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment: Draft January 2014
  - Noninferiority Clinical Trials: Draft March 2010
  - Hospital Acquired Bacterial Pneumonia / Ventilator Associated Bacterial Pneumonia: Draft November 2010
  - Complicated Urinary Tract Infection: Draft February 2012
  - Acute Bacterial Exacerbation of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Final September 2012
  - Acute Bacterial Otitis Media: Final October 2012
  - Acute Bacterial Sinusitis: Final October 2012
  - Complicated Intra-Abdominal Infections: Draft November 2012
  - Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases: Draft July 2013
  - Pulmonary Tuberculosis: Draft November 2013
  - Acute Bacterial Skin and Skin Structure Infection: Final October 2013
- In addition to the updated guidance documents listed above, there are several guidance documents that are being developed, updated, or are planned for development<sup>82</sup>. The topic areas include the following:
- Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

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<sup>82</sup> <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

- Uncomplicated Gonorrhoea
  - Complicated Urinary Tract infections
  - Complicated Intra-Abdominal Infections (cIAI)
  - Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Infections
- The FDA has also published a draft guidance document 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 programmes<sup>83</sup>.
- 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 drugs<sup>84</sup>. Even if therapy already exists, a drug may still be granted fast track designation if advantages over existing therapy are evident, 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.

<sup>83</sup> 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>

<sup>84</sup> 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>

Sponsors may also submit completed sections of an NDA as part of a rolling review for the FDA to begin its evaluation before 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 designation<sup>85</sup>. The goal for completing a priority review of an NDA is six months.
- Qualified Infectious Disease Product Designation: Certain antibacterial or antifungal drugs intended for the treatment of serious or life-threatening infections may qualify for designation as a qualified infectious disease product (the Food and Drug Administration Safety and Innovation Act of 2012 [Public Law 112-144, Title VIII, section 801]). A designation as a qualified infectious disease product provides for regulatory incentives, such as fast track designation, priority review, and an extension of the drug's exclusivity period for certain qualifying products.
- Breakthrough Therapy Designation. An investigational drug that has preliminary clinical evidence indicating the potential for substantial improvement over existing therapies can be designated as a breakthrough therapy (section 506(a) of the FD&C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act of 2012). The designation conveys the fast track program features, as well as intensive FDA guidance on efficient drug development programs
- Proposed Limited Population Antibacterial Drug (LPAD) Program. In December 2013, members of the US Congress introduced legislation<sup>86</sup> to establish a new development program for LPAD. LPAD drugs would be approved to treat limited subsets of patients with serious or life-threatening manifestations of specific bacterial infections where few or no therapeutic options are available. Consistent with the particular benefit/risk profile that exists for such vulnerable patients, LPAD drugs' safety and efficacy could be demonstrated based on more limited data than is required for traditional antibacterial drug approvals. The US Administration has not yet taken a position on the bill. However, FDA will work with Congress to improve the legislation, as requested.

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<sup>85</sup> 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>

<sup>86</sup> H.R. 3742, the "Antibiotic Development to Advance Patient Treatment (ADAPT) Act of 2013, introduced December 12, 2013.

## EU activities (EMA)

### Recent and current activities in the area of antibacterial drug development

- 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.
- EMA has also developed an addendum to the core guidance on the evaluation of medicinal products indicated for treatment of bacterial infections in order to address the most critical expectations for commonly sought indications and to further refine the strategies for development of new antibacterial agents addressing unmet medical needs related to AMR. Following release of a draft document for consultation, a workshop has been held in 2012 and a final version<sup>87</sup> issued in November 2013.
- EMA Infectious Disease Working Party (IDWP) has been established in order 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 working party made up of regulators from some of the national agencies across the EU, an independent advisory group of experts in the field of infectious diseases may be called on 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).

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<sup>87</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/11/WC500153953.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500153953.pdf)

- 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)<sup>88</sup>.
- 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

<sup>88</sup> 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&url=menus/regulations/regulations.jsp&mid=WC0b01ac05800229b9](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&url=menus/regulations/regulations.jsp&mid=WC0b01ac05800229b9)

potential to treat a serious disease and/or fulfils an unmet medical need<sup>89</sup>. 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 medicinal products to be used in emergency situations in response to public health threats recognised either by the WHO 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 product<sup>90</sup>.

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<sup>89</sup> 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](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004136)

<sup>90</sup> 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=WC500004908](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004908)