FDA Task Force on Antimicrobial Resistance: Key Recommendations and Report

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Introduction: Why a FDA Task Force on Antimicrobial Resistance?

Antibiotic resistance (AR) is a growing problem that has recently been identified as a major public health threat and priority by several expert committees, including those of the Institute of Medicine, the American Society for Microbiology, as well as by the U.S. Office of Technology Assessment (1-4). The continuing emergence of difficult to treat or untreatable nosocomial pathogens such as multidrug resistant *Klebsiella,* vancomycin resistant enterococci (VRE), and *Staphylococcus aureus* with intermediate susceptibility to vancomycin and other glycopeptide antibiotics (GISA) threaten the lives of hospitalized individuals and those with chronic conditions and add considerably to health care costs (2,4-11). Even more disconcerting, common community acquired and food borne infections of humans, including those due to pathogens such as *Streptococcus pneumoniae* (12), *S. aureus* (13,14), *Salmonella* (15) and *Campylobacter* species (16), *Mycobacterium tuberculosis* (17), *Neisseria gonorrhoeae* (18) and HIV (19,20) all show trends toward increasing resistance to standard available therapies. Resistant organisms and their genes cross national and regulatory boundaries involving foods, animals, and humans.

The factors responsible for increasing AR and the potential strategies for attacking the problem are complex and encompass a broad range of disciplines. Misuse and overuse of antimicrobials may be driven by unawareness, by inadequate surveillance for resistance and by the misunderstanding of appropriate use by health care providers and by patients and families. At times the welfare of individual patients, usually the health care system's primary focus, may appear to be in conflict with over-arching public health needs. Increased competition in health care may result in limited physician time as well as reduced availability of diagnostic testing which may then contribute to overuse. Marketing practices and industry needs for return from investments may be at odds with the desirability of limited use of broad spectrum and/or newer agents. The use of antimicrobial agents in food animals helps provide inexpensive products for the public but can contribute to the pool of resistant pathogens (21).

In response, better surveillance for resistance and intensive education of health professionals and the public regarding optimum usage of antimicrobials is needed. However, even if all antibiotic use were indeed to become appropriate, resistance would not dissappear. Thus, both continuing research and the development of new and innovative drugs, vaccines and improved diagnostics for infectious diseases will continue to be urgently needed.

FDA has key roles in helping facilitate the development of drugs, vaccines, devices and diagnostics as well as their safe and effective use. In addition, FDA has an important role in informing the public and health professionals both through educational outreach and by assuring

useful and accurate product labeling and appropriate marketing. Various Centers within FDA have already been active in addressing the resistance problem. For example, the Center for Drug Evaluation and Research (CDER) has sponsored Advisory Committee and other meetings to discuss AR and ways to help speed product development including the potential to improve clinical trial procedures for resistant organisms (22). The Center for Veterinary Medicine recently issued a proposed framework for the regulation of antimicrobial drug use in food animals which seeks to reduce the risk of transfer of resistance to humans through the food chain (23). However, the FDA Commissioner and the FDA Centers saw a need to further stimulate and coordinate action to combat AR. To achieve this goal, an Agency-wide Task Force was chartered to develop a clear consensus regarding what, given limited resources, should be the key priorities of the Agency. This document presents the major results of the Task Force's deliberations and represents the Agency's current thinking about how it can best address the antimicrobial resistance problem. In addition, FDA recognizes that managing AR requires ongoing actions by and partnerships with many others, both within and outside of government. To this end, FDA co-chairs (with CDC and NIH) the U.S. multi-department Task Force on Antimicrobial Resistance which is developing a broader "Public Health Action Plan to Combat Antimicrobial Resistance".

Executive Summary

The FDA Task Force on Antimicrobial Resistance (TFAR) was formed with the goals of optimizing FDA's response to the growing public health threat of antimicrobial resistance. The Task Force represented all Centers and offices with interest and expertise in the area and built upon their previous efforts. The Task Force met weekly in the spring of 1999 to consider various content areas, to discuss ongoing agency work and to propose and consider specific action items. The Task Force kept a broad perspective ranging from such issues as the daily workings of the review process to potential new initiatives and approaches involving other agencies and groups. While many other agencies and groups need to be involved in the response to antibiotic resistance, we focused upon issues and areas where we believed FDA should and could play an important part and achieve specific and practical outcomes.

From its meetings, the Task Force developed a list of potential action items which it then ranked. A retreat was then held to consider and reach consensus regarding the most highly ranked proposed actions and to then recommend actions for adoption by the Agency.

The Task Force felt that FDA has responsibilities and the potential to improve public health through actions in 4 key areas:

1) **Promptly and effectively responding to current threats from drug resistance.**

2) **Facilitating and encouraging development and appropriate use of products which help address the issue.**

3) **Facilitating the safe and effective use and thus prolonging the life of products by helping improve the quantity and quality of information available to consumers and health professionals regarding antibiotic resistance and principles of appropriate usage.**

4) **Maximizing and coordinating FDA's scientific research to address needs in antimicrobial resistance.**

The key recommendations of the Task Force in each of these areas are listed below and brief explanations of their background provided. In addition, for future reference, the Task Force report includes other issues and ideas for possible actions which were not given as high or immediate priority. This information should be useful as the Agency moves forward in time and continues to address this issue as it evolves.

Key Recommendations of Task Force

I. An Effective Response to Current Public Health Threats

1) FDA should work to develop an appropriate regulatory framework and explore other options to protect "drugs of last resort" (those drugs which may represent the last line of defense against otherwise resistant organisms). This may include post-marketing surveillance of both use and the development of resistance.

a) FDA should work jointly with NIH, CDC, AHCPR and others to plan and sponsor an interagency Consensus Conference on "Preserving Therapeutic Options for Resistant Organisms"

b) CDER should hold an Anti-infective Advisory Committee Meeting to provide specific input on FDA's role and possible approaches for preserving therapeutic options for resistant organisms.

Discussion:

Ranked of the highest priority overall, the TFAR was concerned that the therapeutic options for resistant infections have become increasingly limited and, therefore, important to protect and preserve for these critical uses. In particular, there are agents, including among them both those recently or previously approved and those as yet unlicensed, which are either the only or among the very few available treatments for life threatening resistant infections. This concept of "Critical (or Class I) Drugs" is also embodied in the Proposed CVM Framework, where they would be given special regulatory status to preserve their usefulness for human medicine. Because these agents are nearly always active against other non-resistant bacteria, and because the number of patients with resistant isolates is usually much smaller, there is a strong market incentive to study and then use the drug against bacteria for which alternative agents exist.

It is widely acknowledged that the rapidity of development of resistance to an agent is increased with the magnitude of its use. Thus, use of these precious drugs of last resort for infections easily treated by other medicine is highly likely to ultimately compromise their efficacy, and, thence, their safety in treatment of serious infections. It was felt that there should be a high priority for monitoring use of and

bacterial resistance against such agents and that such monitoring could be in partnership with industry itself (providing confidential use data) and CDC (coordinating active surveillance). Such monitoring could allow detection of emerging resistance and identification of strategies for addressing such resistance, which could include recommendations for changes in use.

*There are concerns that limiting markets in the absence of compensating incentives (**see 3, below**) could chill future development of new antimicrobials. However, for drugs critical in the treatment of resistant organisms, there was unanimity that FDA should not only explore potential regulatory approaches but also should take a leadership role in bringing together appropriate stakeholders to help define and encourage optimum use of critical agents. This process was felt to be best initiated both through seeking input from the FDA Anti-infective Advisory Committee and through holding a joint conference with other Federal agencies, including NIH, CDC, and AHCPR.*

2) FDA should strongly support effective implementation of the CVM Framework which addresses Antimicrobial Resistance due to food animal uses of antimicrobials.

a) In particular, the monitoring for and response to any threats to the efficacy of drugs critical to human medicine due to food animal uses must be sensitive, timely and decisive.

Comment:

This recommendation is directly linked and related to the above, in that the TFAR felt strongly that appropriate use of antibiotics should be encouraged in both human and veterinary medicine. The Proposed Framework Document seeks to rank drugs by their importance to human medicine and to provide a risk-based framework for their use in food animals. The FDA TFAR strongly supports the concepts embodied in the Framework Document. There was particular concern that certain drugs, of classes currently viewed as critical for human medicin, are already being used in food animals. While the TFAR recognized the complexity of the Framework process, there was strong support for its rapid finalization and implementation in order to fulfill its public health mandate.

II. Facilitation of Product Development

3) FDA should continue to work within the agency and collaborate with outside experts in order to improve and facilitate innovative product development.

a) **FDA should form a high level, inter-center committee to seek outside input and consider issues related to incentives/exclusivity for optimal human and animal drug, vaccine, device (both anti-infective and diagnostic) and biologics development and appropriate use to meet antimicrobial resistance public health needs.**

b) **CDER should move forward in its efforts to facilitate product development by addressing issues such as: use of surrogate markers and pre-clinical data, clinical trials for agents dealing with resistant pathogens and issue appropriate guidance(s).**

c) **FDA should meet with NIH, CDC and others to discuss the possibility of NIH involvement in, or development of, a clinical trial program which addresses otherwise unmet needs in antimicrobial resistance and product development.**

d) **CDRH, with CDER input, should continue to work towards developing standardized guidelines and a management structure for addressing resistance concerns in the review, labeling and promotion of antimicrobial containing devices.**

e) **CDRH, with CDER input, should work with NIH, CDC and others to develop workshops and other possible strategies to stimulate additional interest in rapid diagnostics and susceptibility determination.**

Discussion:

There will continue to be a critical need for innovative product development to meet the threat poised by AR organisms. Desired products include not only new antibiotics, but also vaccines to prevent infections and reduce antibiotic use, and improved, more rapid, diagnostics to identify pathogens and drug resistance. At each step of the product development process, there is room for improvement and innovation.

Under any circumstances, but particularly if appropriate or more limited use of certain antimicrobials is a desired outcome, there may need to be consideration of new economic approaches to help incentivize product development and optimal use. There are special issues involved in encouraging vaccine development, where exclusivity is not currently granted. It was felt that as a first step FDA should form a high level inter-center committee to consider options in this area.

It was also recommended that pre-licensure studies of important new products meeting AR needs be facilitated wherever possible. This includes CDER moving forward its process of identifying and encouraging appropriate uses of innovative preclinical data (e.g. surrogate markers, pharmacokinetic and pharmacodynamic studies) and clinical trial designs to speed product development. It was also felt that the development of an antibacterial clinical trials network, likely under NIH lead, could potentially help facilitate clinical trials that hasten product development and help optimize clinical practice. Such a network could not only work with industry to assist in recruitment of patients with AR infections for trials of new interventions, it could also carry out studies for which the marketing incentives are insufficient (or absent). Such studies could include head-to-head comparisons to determine best therapy (rather than just efficacy), trials of disinfectants, new infection control strategies, studies of generic drugs etc.

Antimicrobial containing devices (e.g. urinary and intravenous catheters, prosthetic heart valves and joints) have been developed with the intention of preventing infections, although clinical safety and effectiveness data for many devices are lacking. However, concerns exist over incorporation of critical drugs into or onto devices, and the potential for the consistent presence of a drug to foster resistance. There is a need for standardized tests to demonstrate safety and effectiveness, and for consistent labeling and promotional claims for such products. Development of a written policy for the collaborative CDRH-CDER review of products that contain both antimicrobial(s) and device(s) will help to insure consistency in product approval.

Finally, the development of multiple new pathogen and resistance detection methods in the research setting has so far had less than desired impact in the clinical laboratory. While many of the difficulties in the development and transfer of new diagnostic technologies involve issues such as cost and quality control, the potential payoff in terms of enhancing appropriate use of antiinfectives is tremendous. There is a great need for rapid tests to identify the presence or absence of infection, if infection is present whether it is bacterial, and, if bacterial, whether it is resistant. The TFAR felt that FDA should work with other PHS agencies to enhance interest and speed progress in this field.

III. Facilitating the Safe and Effective Use of Antimicrobials

4) CDER should complete, and the Agency strongly support, the proposed antimicrobial resistance labeling.

Comment:

Product labeling offers FDA the opportunity to communicate important facts about drug safety and efficacy and provides key information that should be adequately presented in promotional activities. Antimicrobial resistance is an important potential adverse effect of antimicrobial usage and may compromise efficacy. Adherence to basic principles of antibiotic use can reduce the likelihood of encouraging resistance. For example, antibiotics are ineffective and contraindicated in viral infections. Also, where possible, antimicrobial use is best guided by local epidemiology and resistance patterns. CDER has been considering required labeling for all antibiotics to include key information about resistance and to encourage judicious, safe and effective use. The Task Force strongly supports this effort.

5) **FDA should work with NIH, CDC, AHCPR and others (e.g. health professionals, industry, health care organizations) to organize a conference or other process to develop and promulgate "Basic Principles for Antimicrobial Use".**

Comment:

This action is closely linked to the set of issues embodied in the proposed antimicrobial labeling, but extends the educational effort further and should include a full range of stakeholders. There is a need to develop a shared consensus on general principles for antimicrobial use which can be included in health professions education, used by health systems and providers, and by government agencies. Such a consensus process and the principles agreed upon would be very useful as benchmarks for quality care and in the future development of specific strategies for addressing emerging issues in anti-infective therapy.

6) **FDA should work towards assuring that patient educational materials are provided with each antibiotic prescription and which include content stressing appropriate antimicrobial use. FDA should use a variety of means (e.g. meetings, a new Website feature with outside links, publications) to better provide enhanced and consistent information to consumers and professionals regarding antimicrobial use and resistance, new antimicrobial approvals and related issues.**

Comment:

The effort to provide information about antimicrobial products and to address the resistance problem is complex and involves many partners. As part of its continuing efforts to better serve consumers and professionals, FDA is uniquely positioned to play an important role in providing accurate, consistent and balanced information. Medication information provided by the pharmacist with each prescription represents

an important educational opportunity. FDA should work with the health professions, academia, pharmacist groups and others to design messages for these materials which stress appropriate antimicrobial use. It may be possible to accomplish this in conjunction with current private sector providers of pharmacy educational materials.

In addition, both traditional (e.g. meetings, liaisons with existing groups, medical journals) and less traditional or newer approaches (e.g. World Wide Web, women's and parents' magazines) should be used to make detailed information on appropriate use of approved antimicrobials widely available and well linked to other important sources. It may be particularly useful to the health professions for FDA to promptly post information on newly approved drugs and the clinical trials that led to their approval.

7) **CDER should develop a Guidance Document regarding both direct-to-consumer and professional promotion of antimicrobials which deals with key resistance issues and encourages appropriate promotion to preserve safety and efficacy of approved products.**

Comment:

Direct-to-consumer and professional promotion of antimicrobials are both significant sources of information to the public and the profession, respectively. Issues of antibiotic resistance and principles of appropriate antibiotic use are only inconsistently addressed. Some sponsors have included very helpful information to encourage appropriate use of their products and to minimize the development of resistance (e.g. stressing that most earaches are not caused by bacterial infections and do not require antibiotics). The requirement for key information on antimicrobial use for inclusion in product labeling should be followed by the development of a more detailed guidance document which should serve to enhance the quantity, quality and consistency of information about resistance which reaches the intended targets.

IV. Coordinating FDA's Scientific Response to Antimicrobial Resistance

8) **FDA should form an inter-center standing committee to identify and prioritize FDA research needs and goals concerning antimicrobial resistance. This committee should include laboratory scientists and clinicians from both veterinary and human**

medicine. The committee should perform an initial and periodic assessment of FDA AR research to help assure that it effectively meets the Agency's goals and fulfils clear and unmet Public health and regulatory needs.

9) **This committee should also coordinate FDA resistance research activities with those of other Agencies (e.g. CDC, USDA, EPA) and arrange for the periodic outside review of FDA's antibiotic resistance research as a whole.**

Comment:

While much research on AR is performed at universities and in industry, FDA can play an important role, particularly in addressing questions underlying science-based regulatory activities. There would be value added in a periodic articulation of the underlying unmet regulatory and clinical needs and linkage of these needs to the development of the research agenda and its priorities. FDA has important scientific resources invested in AR and related areas and FDA scientists have made important contributions to the field. The spectrum of such research ranges from the basic (e.g. mechanisms of resistance induction and transfer related to food animal use of antimicrobials) to the applied (e.g. improved detection of resistant pathogens in regulated food products). In hearing about the efforts of multiple centers, it also became clear that coordination of AR research, both within FDA and with sister government agencies and academia, is currently largely informal. Finally, periodic external review of FDA AR research was recommended as was better coordination and communication with other PHS Agencies.

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