Regulatory Plan to Combat the New Plague of Antibiotic Resistance

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July 2001

1. The purposes of this paper are to provide the reader with:

a. The seriousness of this public health issue related to antibiotic resistance (Part I)

b. A basic understanding of the biological issues involved in antibiotic resistance (Part II)

c. Factors that have contributed to increase in antibiotic resistance in the recent past (Part III)

d. A regulatory plan to combat antibiotic resistance (Part IV)

PART I: ANTIBIOTIC RESISTANCE: THE NEW PLAGUE

Man versus Microbes: From Victory to Impending Defeat

Victory: The three major causes of death in 1900 in the US were tuberculosis, pneumonia and gastrointestinal infections. With the introduction of antibiotics into clinical practice, starting with penicillin in the 1940s, there was a marked decrease in life threatening infections (2). In 1975, the Surgeon General of the United States declared victory over microbes with the statement the time had come "to close the book on infectious diseases" (3).

Impending Defeat: The seriousness of the problem is that, in simple terms, a bacterial infection, not susceptible to antibiotics because of resistance, can result in the death of the infected patient . The recent emergence of antibiotic resistance raises the specter that it may not be possible to successfully treated millions of infected patients, resulting in high mortality and morbidity (4). The Surgeon's declaration of human victory over microbes has proven to be premature (5). Recent statistics, which show an increase in the failure to successfully treat infected patients (6), justify these concerns. Mortality rates due to infectious diseases increased 58% between 1980 and

1992 (7). Further, the Center for Disease Control (CDC) estimates that more than 50% of the infection related deaths involve resistant bacteria (8). Epidemiological data show that an estimated 1.4 million salmonella infections occur in the United States (9); most of these occur in children and the elderly and about 600 of these patients die of their infections (10). Sepsis (11) is an infectious disease complication that is encountered in about half a million patients every year with an annual death rate of 175000 (12). Nosocomial (hospital acquired) infections increase health care costs in hospitalized patients by $4.5 billion annually. (13) Other reports estimate the cost of extended hospital care resulting from antibiotic resistance to be $30 billion. (14)

The devastating infectious diseases episodes, caused by viruses, from history should serve as a caution. First was the influenza pandemic of 1918 that resulted in 500,000 deaths in the US and 20 million deaths across the globe in one year (15). Second is the ongoing infection with HIV infection that has claimed about 14 million deaths so far (16). There is fear that antibiotic resistance could lead to epidemics of non-treatable bacterial infections. For example, vancomycin is the only effective drug currently available for some life-threatening infections caused by gram-positive cocci (17). Results from the CDC National Nosocomial Infections Surveillance system showed that vancomycin-resistant enterococci (VRE) increased about 25-fold between (from 0.3% to 7.9%)1989 and 1993 (18). There was a corresponding increase in VRE from clinical samples obtained from intensive care unit patients (19). Increasing fear that vancomycin, the last line of defense against certain bacteria, would also become ineffective, caused the CDC to publish guidelines in 1994 for the prudent use of vancomycin so as to prevent or minimize development of antibiotic resistance(20). A retrospective analysis of vancomycin use in one hospital as per these CDC guidelines, showed vancomycin use was inappropriate in about 60% (81 out of 135) of the patients (21). These guidelines discourage the empiric use of vancomycin in patients with febrile neutropenia (22). This study found that 14 of the 81 subjects received vancomycin for this condition (23). In many instances, vancomycin therapy continued even after culture results suggested other appropriate drugs.

Federal legislation to combat this problem at the national level (24) has been proposed.

Details (25) in this proposal, some of which are cited below, illustrate these concerns:

Item (9) (Sec. 2 of Findings) reads "Antibiotic resistant bacteria selected in animals can reach humans and pass their resistance to bacteria pathogenic to humans, or if

pathogenic themselves, can cause disease that is not easily treatable, prolonging recovery."

Item (10) (Sec. 2 of Findings) reads, " Statistics have shown that antibiotic resistance can cause the total costs of inpatient care to be more than double the direct costs of such care."

Item 11 (Sec. 2 of Findings) reads, " Expenses incurred by hospitals around the Nation have risen to nearly $1.3 billion per year as a result of six ordinary types of resistant bacteria."

PART II: BASIC MICROBIOLOGICAL ISSUES IN ANTIBIOTIC RESISTANCE.

The purpose of this section is to provide the reader with a basic understanding of bacterial biology and how bacteria combat antibiotics. This information will familiarize non-biologists with a brief introduction to bacterial nomenclature and provide a basis for understanding the biological bases of antibiotic resistance. Such knowledge is crucial in proposing strategies to combat the problem.

Classification of bacteria:

Three basic shapes of bacteria have been used to distinguish bacteria; the common shapes are rod- shaped bacillus (meaning little staff), spherically shaped coccus (meaning berries, plural: cocci) and spiral(26).

Bacteria are also classified based on their staining properties into two categories, namely, Gram-positive and Gram-negative. This staining property was discovered by Hans Christian Gram of Denmark in the late 1880s (27) who found that certain bacteria stained purple when exposed to the dye he was using (hence classified as Gram-positive) and some did not (Gram-negative). The staining property or the lack of it is attributed to the composition of the bacterial cell wall.

Development of Bacterial Resistance to Antibiotics

Resistance is a defense (survival) mechanism for bacteria against itself and antibiotics. This is not surprising since the term "antibiotic", is strictly defined as a natural substance made by one microorganism that kills or inhibits the proliferation of another microorganism (28). The term now includes man-made chemicals kill microbes (synthetic antibiotics, such as methicillin). Therefore, an organism in order to protect itself from self-created toxins, have developed mechanisms to protect itself. Protection

is provided by genes present in the bacterial DNA that enable the production of that produce protective proteins or enzymes kill other organisms. It has been shown that resistance genes existed even before the development and clinical use of antibiotics. A study of fecal samples from Kalahari busmen who were not exposed to antibiotics and wild animals from Zimbabwe (then Rhodesia) revealed resistance bacteria, though in low numbers (29).

Resistance Development: Bacteria use several biochemical ways to develop resistance to antibiotics. Some common mechanisms used by bacteria to acquire resistance are discussed below, briefly.

Mutation. Mutation is process by which the genetic make up of the cell is altered as it undergoes repeated divisions. In laboratory condition, the doubling time is about 20 minutes for many bacterial species. The doubling time is the time for any given number of existing cells to double. It was originally thought that bacteria become resistant primarily by mutation. The resulting new genes facilitate the production of proteins that protect the bacteria from antibiotic action. Since mutation is a relatively slow process (30), development of resistance was not considered a serious problem. It was the first reported multi-drug resistant incident in 1959, that lead to realization for the first time that genetic change in bacteria occurs by other mechanisms (31) (discussed in the following section)

Gene exchange: A second method by which bacteria acquire resistance is by transfer of resistance genes between themselves. Gene exchange, as the term implies, is transfer of genetic material between bacteria. In this exchange, bacteria provided each other with genes that become part of their genome. Subsequently, both species produce proteins that protect them from the effects of antibiotics. It is the primary means by which organisms susceptible to antibiotics become resistant. Gene exchange or inter-bacterial transfer of resistance genes, among bacteria "is so pervasive that the entire bacterial world can be thought of as one huge multi cellular organism in which cells interchange their genes with ease" (32). Common mechanisms for gene exchange are discussed below.

Conjugation (33): This is essentially a type of bacterial mating where a bacterium containing a plasmid (34)(the "donor") makes contact with another bacterium (the acceptor) through a "pilus" which is a long, filamentous structure made of proteins. The donor then passes on a copy of the plasmid to the other bacterium. If the plasmid contains resistance genes to a particular antibiotic, then the acceptor bacterium, like the donor, becomes resistant to that specific antibiotic. As can be inferred, such exchange of plasmids can result in the bacteria resistant to many antibiotics (multi-drug resistant species). Genes on plasmids are more readily transferred than genes on the chromosomal sites (35). Such mechanistic knowledge provides insight into the

relative probability (which type of resistance is easier to acquire) of development of antibiotic resistance. Ease of resistance transferability should be a factor in determining imposing regulatory restrictions on antibiotic use.

Transposition (36): Transposons are also called "jumping genes", which are located on fragments of DNA smaller than plasmids. These genes found on plasmids can transfer ("jump") from one site on a plasmid of one bacterium to another plasmid of a second bacterium. Gene transfer is accomplished without the need for incorporation of the entire plasmid between bacteria. Transposition offers advantages over plasmids in spreading resistance genes among bacterial populations. (37)

Transduction (38): is the process by which bacterial viruses called bacteriophages (phages for short) transfer genes after they enter a bacterial cell. After a phage attaches itself to a site inside the bacteria, it transfers its DNA into the cell. The phage can pick up pieces of the host chromosome and thus alter its genetic makeup. Gene transfer occurs when the genetically modified phage enters another bacteria and transfers its DNA into the new host.

Transformation (39) :In this type of gene transfer, one bacterium picks up DNA fragments released by another bacterium. These DNA fragments are then incorporated into the genetic make up of the recipient bacterium.

A bacterium that possesses or acquires resistance genes from other bacteria protects itself from the action of antibiotic in many different ways. Common mechanisms by which bacteria make antibiotics ineffective are described below (40).

Decreased Entry into the Cell

Antibiotics must enter the bacterial cell to exert its action. Entry is accomplished by two major mechanisms: (1) diffusion and (2) carrier-mediated transport.

Diffusion, sometime called "downhill transport", is a common biological mechanism of transport of drugs in biological systems where it moves ("diffuses") from a region of high concentration to a region of lower concentration. Therefore, when bacteria are exposed to an antibiotic present in the blood or tissue (region of higher concentration), it will enter the bacterial cell (region of lower concentration) by diffusion. Bacteria can decrease the diffusion of the antibiotic (i.e., decrease permeability of the antibiotic) by making it difficult for the antibiotic to penetrate the cell-wall structure, for example, by closing certain channels (openings in the cell wall) through which drugs gain entry into the cell (41). However, since diffusion is concentration driven,

increasing the blood concentration of the antibiotic by giving larger doses of the drug to the patient is a successful approach to combat this type of resistance in certain cases.

Carrier-mediated transport occurs when proteins on the bacterial cell wall (one major purpose of such proteins is carry nutrients into the cell) also carry the antibiotic into the cell. Cell wall proteins of resistant bacteria do not transport the antibiotic and thus deny entry of the antibiotic into the cell.

Removal of antibiotic from within the cell

The effects of the antibiotic can be minimized or prevented if the antibiotic is quickly "pumped out" of the cell, soon after its entry into the bacterial cell. Proteins within the cell serve as such "efflux" pumps" and protect bacteria from the effects of the antibiotic (42).

Inactivation of the antibiotic

Enzymes present in the bacterial cell can inactivate the activity of the antibiotic by breaking down its structure (43). These enzymes are very specific for a given antibiotic. Penicillins and cephalosporins are good examples where bacteria destroy penicillins by specific enzymes called pencillinases and cephalosporins by cephalosporinases. There are more than a dozen such enzymes for each of the two antibiotics (44).

Target alteration

Antibiotics work by attacking some biochemical target (often it is an enzyme inside the cell, as in the case of quinolones and rifampin) essential for the survival of the bacteria. The first step is binding of the antibiotic to the target. In a resistant bacterial species, that enzyme is slightly modified such that it makes it difficult for the antibiotics to bind to the enzyme, which maintains its biological functions despite the modification. (45) It is important to note the antibiotic, because the bacteria do not destroy it, remains in the environment and will continue to kill susceptible organisms, providing a selective advantage to resistant organisms.

Multi-drug Resistance

When a bacterium acquires many resistant traits, then they become resistant to more than one antibiotic. Multi-drug resistance among bacteria has become the rule, and not

exception, posing life-threatening consequences for infected patients. This problem was first reported in 1950 from Japan where bacteria (Shigella dysenteriae) linked to an outbreak of dysentery were resistant to four antibiotics (tetracycline, sulfonamide, streptomycin and chloramphenicol) available at that time (46). A more recent example is the serious problem of tuberculosis facing health authorities in New York City. (47)

PART III: DEVELOPMENT OF ANTIBIOTIC RESISTANCE

Physicians have unrestricted ability to prescribe medication for their patients ("out-patients) during office visits (48). However, over the last 2-3 decades, the study of drugs, such as pharmacology (the study of actions of the drug) and therapeutics (proper use of drugs) have been de-emphasized in medical curriculum. Therefore, not surprisingly, physicians often rely on information provided by the drug salesman in selecting antibiotics. (49) . This has led to inappropriate prescribing of antibiotics by physician, which is the primary cause of antibiotic resistance (50). Such reliance results in (1) the over prescribing of more expensive broad spectrum antibiotics, (2) the selection of ineffective antibiotic and inappropriate doses (3) the use of antibiotics for viral infections and (4) substitution of antibiotic therapy for surgery (51). It has also been reported that about half of the 150 millions prescribed annually are "unneeded" (52). Such over use and misuse of antibiotics poses significant risk of developing microbial resistance to antibiotics.

There are also patient pressures that make the physician prescribe unnecessary antibiotics. In addition, there are also malpractice concerns that make the physician prescribe antibiotics ("defensive medicine"). In one case, a patient with respiratory distress was moved to the neonatal intensive care unit but was not given any antibiotics. Later, the baby died of a Group B Strep infection. The plaintiff was awarded $ 2.5 million for negligence on the part of the physician for improper diagnosis and treatment. (53). In another case, a dentist was held liable for failing to prescribe prophylactic antibiotics prior to tooth extraction. The patient developed bacterial endocarditis (54) and had to undergo heart valve replacement. (55)

How does misuse of antibiotics cause antibiotic resistance (56)? First, antibiotic use provides a selective advantage to resistant bacteria. Both resistant and susceptible bacteria compete for nutrients in their environments. Antibiotic use kills all the susceptible organisms, resulting in an environment where the resistant bacteria flourish. Since bacteria readily exchange genetic material among each other (see supra), an increase in the number of resistant bacteria results in a corresponding increase the probability of transfer of resistance properties to non-resistance organisms, resulting in overall increase in resistance to antibiotics.

Clinical experiences, from United States and abroad, show that antibiotic resistance can be reduced by judicious use of antibiotics . Surveillance, restricted use and education have contributed to significant decrease in antibiotic use and a concomitant decrease in antibiotic resistance in Mount Sinai Hospital (57). The first prong of this three-prong approach required that antibiotics be classified into restricted and unrestricted groups (58). Antibiotic prescribing requires consultation with and approval of an infectious diseases specialist. The second prong was educational where the hospital provided physicians with published information on judicious antibiotic use. The third prong was surveillance of antibiotic use and emergence of resistant infections by prospective and retrospective audits of antibiotic prescriptions and analysis of antibiotic use patterns.

The current infectious disease reporting system in the United States is a responsibility of each state (59). It decides the disease or conditions to be reported by health care professionals. The states report these findings to the Center for Disease Control and Prevention (CDC) on a voluntary basis. Budgetary constraints have decreased local and state support for infectious disease surveillance (60); for example, in 12 states, there are no personnel dedicated to surveillance of food-borne diseases in spite of evidence that such diseases may be on the increase (61). The value of such a surveillance system can be seen from a 1993 episode of an outbreak in 4 western states of an E- coli infection caused by hamburger contaminated with this bacteria. More than 600 cases were reported, with 56 instances of kidney failure and 4 fatalities. The state of Washington, which had established a system for detecting dangerous E. coli, was able to quickly identify the culprit organism and initiate a rapid recall of 250,000 hamburgers contaminated with this bacteria; this resulted in termination of the outbreak. However the cause of the outbreak in Nevada, which happened mostly before that in Washington, went undetected till officials in Washington state reported the cause of the outbreak.

Drug development is an extremely expensive and time-consuming matter. (62) Economic gain associated with the widespread or overuse antibiotic would make it less likely that a manufacturer of antibiotics would take action to restrict the use of antibiotics.

PART IV: REGULATORY STRATEGIES TO COMBAT ANTIBIOTIC RESISTANCE

The discussion presented (supra part III) strongly support the hypothesis that regulatory restrictions comprise the only plausible remedy to combat the growing problem of increased resistance of bacteria to antibiotics. Development of successful

strategies to combat antibiotic resistance must be based on a sound knowledge of the factors that have been responsible for the development of such resistance. Many studies (supra, part III) have shown that improper of use of antibiotics is the single most important cause for development of antibiotic resistance. Studies also show that proper use of antibiotics can be effective in reducing the incidence of antibiotic use (supra, part III). Therefore regulatory schemes to combat this problem should aim to encourage appropriate use of this important class of drugs. Part IV will address these issues in detail including a discussion of existing regulatory schemes and reasons for their failure in dealing with this serious public health problem.

Regulatory Control of Physician Prescribing: Improper use of antibiotics in the outpatient setting is one major cause of antibiotic resistance (63). Therefore, to be effective, regulatory strategies to combat antibiotic resistance should include measures to restrict use of this class of drugs in the outpatient setting. There are two approaches to achieve this goal.

A. Physician Sanctions by State Medical Boards to combat Antibiotic Resistance

Physicians are licensed to practice in a state by its the medical board. Therefore state medical boards should, in order to prevent or minimize antibiotic misuse, pass regulation that would make such misuse punishable by license suspensions or revocations (64). For example, in one case, a physician's license was suspended for improper dispensing of drugs (65). The consequence of antibiotic misuse, namely antibiotic resistance is a situation were the " cure is worse than the disease". The court used such language in sanctioning an Ohio physician in charge of a weight loss program. (66). More states need to pass regulations that sanction physicians for inappropriate use of antibiotics, such as those enacted in Ohio (67)

B. Modifications of the Controlled Substances Act (68) to control antibiotic resistance

This Act seeks to control the use of drugs with potential for abuse. Drugs are classified into 5 schedules according the potential for abuse and psychological dependence, safety, and acceptability for medical use(69). Sale of Schedule I drugs is prohibited in the United States (70). The problem of antibiotic use is obviously different from the problem of drug dependence (71). This recent publication argues that close monitoring of antibiotics would not prevent antibiotic misuse (72). However, the author recognizes that re-classification of a drug from Schedule III to II results in a significant decrease in its use (73). Since it has been shown that misuse of antibiotic is a major cause antibiotic resistance (74), "scheduling" the use of antibiotic on the regulatory model for controlled substances should help prevent or minimize antibiotic resistance. The common aspects of abuse, whether it is due to addiction (controlled substances) or ignorance (antibiotics), are that both issues are serious

public health issues. The objective of regulation is to restrict antibiotic use to only those situations where they are essential for patient therapy. Patient well being is not compromised. Therefore, new regulations (see infra) should be beneficial.

The objective of the new regulation would be to also monitor antibiotic use in the outpatient setting. Such regulation will serve as a constant reminder to health care professionals of the need for judicious use of antibiotics to avert a potential public health calamity. Such information will be useful in understanding the epidemiology of infections at the national level. The following antibiotic classification (the word "schedule" is intentionally avoided to prevent confusion with controlled substances) and reporting requirements are proposed (in italics).

New Classifications for Antibiotics

Class I antibiotics: All newly approved (75) and those antibiotics that are the last line of defense (such as vancomycin) belong to this class.

Class II antibiotics: All broad-spectrum antibiotics shall be included in this class.

Class III antibiotics: All narrow spectrum antibiotics belong to this class.

Reporting Requirements

As with Schedule I and II controlled substances (76), all antibiotic prescriptions (Classes I, II and II) shall require a triplicate order with one copy forwarded to the CDC, one to be kept by the prescriber and the other by the dispenser, subject to inspection by the CDC.

Such classification can be expected to result in more judicious use of antibiotics. The mandatory reporting system will provide demographic data on such important issues as physician prescribing habits and antibiotic use in a given area. When cases of antibiotic resistance are reported, the CDC can take corrective measures by providing alerts to the health care teams in the locality. Implementation of proposed regulation will require additional funding for the CDC, an issue that has been recognized in the proposed bill in the Congress to combat antibiotic resistance. (77)

Modification of Medicare Laws to control antibiotic use

Hospitals, as is commonly l known, comprise the second major location of heavy antibiotic use. The outbreak of nosocomial (hospital-acquired) infections is a serious

problem, a result of antibiotic misuse(78). This experience is consistent with observation in outpatient population discussed (see supra). Federal Medicare law and guidelines of the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) regulate hospital standards. For twenty years (between, 1966 and 1986), Medicare regulations (Conditions of Participation, COPs) mandated that each participating hospital have a scheme to control antibiotic use within the hospital (79). The most specific of these conditions that dealt with antibiotic use required the hospital to establish an infection committee whose many functions included "control of indiscriminate use of preventative antibiotics in the absence of infection, and the use of antibiotics in the presence of infection is based on necessary cultures and sensitivity tests." (80)

However in 1986, these regulations were modified to eliminate controls on in-hospital antibiotic use. The reason for proposing change in existing rules (81) was stated in a general manner as "[a] part of the Departments regulatory relief efforts, and is designed to reduce Federal requirements, simplify and clarify regulations, and provide maximum flexibility in administration, while protecting patient health and safety" (emphasis added). In retrospect, though there are other contributing factors, these modifications appear to have been a mistake, since antibiotic resistance has increased considerably since 1986 and has severely compromised patient health and safety. It has been speculated that these changes were to conform to JCAHO regulations, which require infection control but do not impose any restrictions on antibiotic use (82). This speculation appears valid since the revised regulations read:

Because of the enormity of the [hospital] problem, we are proposing . . . to elevate control provisions to a separate Condition of Participation. The proposed revision would place more accountability on hospitals to prevent, control, and report hospital infections, and less emphasis on the number of persons necessary to accomplish the task.

The final result was that the infection committee was replaced by one or more infection officers (83).

It is worthy of note that these COPs, abandoned in 1986 by HHS, are very similar to the three-prong method of surveillance, restricted use and education that was found to be successful in combating antibiotic resistance in a hospital setting (84). Therefore, it is proposed that COPs as they existed in 1966 be re-codified with some revisions: (See below, italics)

The Hospital provides a sanitary environment to avoid sources of transmission of infections. The factors explaining the standard are as follows:

An infection committee composed of members of the medical [, pharmacy (85)] and nursing staffs and administration is established and responsible for investigating, controlling and preventing infections and [antibiotic resistance] in the hospitals. Its responsibilities include:

The establishment of written infection control and [antibiotic resistance] measures; and

The establishment of techniques and systems for discovering and reporting infections [and antibiotic resistance} in the hospital.

Written procedures govern the use of aseptic techniques and procedures in all areas of the hospital.

To keep infections [and antibiotic resistance] to a minimum, such procedures and techniques are regularly reviewed by the infection committee, particularly those concerning [antibiotic use], food handling, laundry practices, disposal of environmental and patient wastes, traffics control and visiting in high risk areas, sources of air pollution, and routine culturing of autoclaves and sterilizers.

There is a method of control used in relation to the sterilization of supplies and water, and a water policy requiring sterile supplies to be reprocessed at specified periods.

Formal provisions are made to educate and orient all appropriate personnel in the practice of aseptic techniques such as hand washing and scrubbing practices, proper grooming, masking and dressing care techniques, disinfecting and sterilizing techniques and the handling and storage of patient acre equipment and supplies.

There are measures which control the indiscriminate use of preventive antibiotics in the absence of infection, and the use of antibiotics in the presence of infection is based on necessary cultures and sensitivity tests.

Continuing education is provided to all hospital personnel on the cause, effect, transmission, prevention and elimination of [inappropriate antibiotic use and] infections.

A continuing process is enforced for inspection and reporting of any hospital employee with an infection [or antibiotic resistance] who may be in contact with patients, their food or laundry.

Regulatory Modifications in Post-Marketing Reporting to Reduce Antibiotic Resistance (86)

Introduction: The manufacturer of an approved New Drug Application (NDA) (which includes all prescription drugs such as antibiotics) is required to provide the FDA with prompt reports regarding the safety and efficacy of the drug when introduced to the population at large. Specifically, "serious adverse reactions" (87)are to be reported promptly. Such mandatory reporting has the potential to be useful as a mechanism to obtain information about antibiotic use and resistance. Unfortunately, the definition of what constitutes "serious adverse reaction" does not currently include antibiotic resistance. Necessary modifications to include reporting of antibiotic resistance will be discussed later in this section (see infra). First, a brief description of the drug approval process is provided. An understanding of this process will provide the reader with the public health (pharmacological) need for post-marketing reporting.

The drug approval process: The Food and Drug Cosmetic Act (FDCA) (88) regulates drugs (89) for human use in the United States Antibiotics come under the definition of a drug according to the FDCA and are approved for use and regulated under section 505 (90) of the FDCA. These regulations require that, before a new drug can be marketed in the US, the applicant must obtain FDA approval; approval is granted or denied based on the submission by the applicant of a NDA, which contains extensive information about the drug whose approval is sought. Briefly, an NDA consists of results from (a) pre-clinical (91) (animal and in-vitro (92)) studies to determine safety for human use and (b) clinical (93) (Phase I, II and III) studies involving healthy human subjects and patients regarding safety and efficacy of the drug candidate. Phase I studies usually involve about 20-80 healthy human subjects. Phase II investigations involve several hundred patients, while Phase III testing involves up to several thousand patients. Once the drug is approved it has the potential to be used in millions (in fact the entire population of the US) of subjects. Therefore, adverse effects not observed in the relatively small number of patients involved in the pre-approval studies, can come to light when used in the population as a whole.

Legal issues: Post-marketing requirements arose more out of practice than by regulation. Therefore, the FDA has no history of specific authority to require Phase IV studies as a condition of drug approval. However, the position of the FDA is that there is statutory support for this practice since the agency has specific powers (94)regarding grounds for the withdrawal of an approved drug (when it is found unsafe), which requires post-marketing information. Though legally tenuous, the FDA approved levodopa in 1970, used to treat Parkinson's diseases, on the condition that manufacturer conduct long-term studies about the drugs safety (95).

The agency also has general powers (96) with respect to enforcement of the FDCA, which aims to ensure two issues of public interest, namely the safety and efficacy of drugs on the market.

The socio-political issues, primarily those relating to the AIDS epidemic resulted in the establishment by the FDA of procedures to accelerate the drug approval process in order to meet the public need (and demand in some instances) for accelerated drug approval for life threatening illnesses, especially anti-AIDS drugs. In 1992, the requirement for Phase IV studies became mandatory with this accelerated drug approval program(97). The FDA started to approve (accelerated drug approval) drugs without the benefit of full clinical studies (especially Phase II and III). This approval was based on indirect evidence of drug effect referred to in the clinical literature as "surrogate endpoints". For example, in AIDS patients, the number of a specific type of blood cells (CD+) is an index of the patient's immune function. So a drug that increases CD+ cells in blood (called the surrogate marker) in AIDS patients can be taken as its ability to enhance the patients' immune function. While it takes years to clinically test for improvement in immune function, improvement in CD+ cells in blood can be tested in a relatively shorter time. Such accelerated approval was, based on reasons of drug safety and efficacy, specifically conditioned on completion of post-marketing studies. (98)

Information to be provided as part of post-marketing reporting, also termed Phase IV studies (99), addresses issues such as (1) additional safety data (2) efficacy data (3) detect uses or abuses of the drug and (4) effectiveness under widespread use. Antibiotic resistance can come under items (2), (3) or (4) in the preceding sentence. Antibiotic resistance results in poor efficacy of the drug (items (2) and (4) of the last sentence); improper or under usage could be classified as abuses of the drug (item 3, last sentence). At present, there is no nation wide reporting system for incidence of antibiotic resistance in the US. Such information will be most beneficial in identifying details such as frequency and extent of antibiotic resistance in specific regions or hospitals.

Failure of drug therapy is one of the listed adverse drug events (ADEs) that need to be reported in post-marketing drug surveillance (100). Failure of a patient to respond to antibiotic therapy is the main consequence of antibiotic resistance. Therefore, antibiotic resistance, which results in therapeutic failures, would come under the definition of ADE. Further, ADEs are sub-classified as (a) life-threatening (b) serious (c) and unexpected ADEs (101). Antibiotic resistance could come under any of these sub-classifications. However, the definition of serious ADEs best describes antibiotic resistance because it includes death, life threatening ADE, or prolongation of existing

hospitalization (102). While specific examples of drug-related medical problems are cited, antibiotic resistance is not so listed. At present, ADEs, based on statutory language, could be easily interpreted to include only problems resulting from direct use of the drug. Antibiotic resistance may go unreported since this phenomenon may be considered not to be a direct result of the use of the antibiotic. It is suggested that existing regulation be modified to include antibiotic resistance as a serious, unexpected ADE (see infra).

The existing regulation for post-marketing reporting requires the manufacturer, packer or distributor to report any ADE to the FDA within 15 days (103). The report is to be filed on FDA Form 3500A (104); this form has 7 categories (check boxes) in section B to identify the "Outcomes attributed to adverse event" (105). The categories do not include antibiotic resistance. The inclusion of the antibiotic resistance category is recommended (see infra).

Once a report of a serious, unexpected ADEs is made, the manufacturer, packer or distributor is also required to conduct a quick follow investigation and report the findings to the FDA (106) The FDA has discretionary power to ask for additional information. (107) Therefore, it is recommended that antibiotic resistance be classified as belonging to the serious, unexpected type (see infra).

The FDA also has broad responsibility for the safety and efficacy of all drugs on the market (108) . Modifications are recommended to highlight the issue of antibiotic resistance. (See infra)

The following revisions are recommended to the FDCA :

Revisions to 21 CFR § 310.305

Additions of a new definition to 21 CFR § 310.305(b)

Antibiotic Resistance Adverse Drug Event: Any form of antibiotic resistance by bacteria shall be considered a serious, unexpected adverse drug event. All patients whose infections are treated with antibiotic(s) and (1) fail to respond, (2) require hospitalization because of antibiotic failure (3) require multiple antibiotics to treat their infectious or (4) show presence of organisms resistant to antibiotics shall be reported to the FDA.

Antibiotic resistance. Clinical experience of antibiotic failure or suspicion of antibiotic failure shall be considered to a serious, unexpected adverse drug event, under the meaning of this section.

Revisions to Form 3500A(section B) (109) (21 CFR § 310.305(d))

A check-off box identified as 'Antibiotic Resistance' should be added

Revisions (in italics) to (21 USC § 355(k))

"In the case of any drug for which an approval . . . is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data and information, received or obtained by such applicant with respect to such drug . . . of this section. For each antibiotic, the applicant shall provide, on an annual basis, to the Secretary information on details of clinical experience with antibiotic use. Examples of information include but not restricted to patient information, history of antibiotic use such as drug(s) used and duration of use, death as a result of infectious disease, extended hospitalization due to infectious disease, history of antibiotic resistance either in the patient, locality of residence or hospital where patient was treated.

Regulatory control of antibiotic use in food-animals to combat antibiotic resistance

Transfer of antibiotic resistance from animals to humans is another source for the growing problem of antibiotic resistance. (110) Sub therapeutic doses of antibiotics were used to ward off diseases in chickens, starting in the in 1930. (111) The discovery in the early 1950s that small amounts (less than therapeutic doses) of antibiotics in animal feed enhanced growth in food animals such as chickens and cattle resulted in routine use of antibiotics in such animals (112). The economic advantages of a larger animal or bird to farmers were a great financial incentive that led to indiscriminate of antibiotics in these animals. It is estimated that about 80% of the antibiotics used in animals is for growth promotion and not for treating infectious diseases (113). The rapidity with which resistance developed in the chickens is illustrated by a study conducted in the 1970s (114). Within 24-36 hours after the introduction of oxytetracycline into the chicken feed, E. Coli found in the intestines of the antibiotic-exposed chickens had become resistant to tetracycline. Within 3 months, these organisms also became resistant to other antibiotics such as ampicillin, streptomycin and sulphonamides, though the birds were not exposed to none of these antibiotics. As with the chickens, E. Coli found in members of the farm family was largely resistant to tetracycline and other antibiotics in about 6 months after introduction of the tetracycline into the feed of chickens. None of the family members had ingested any antibiotics or eaten the chickens fed oxytetracycline in their feed. Development of such resistance is not limited to chickens of the United States (115); reports from Europe involving pigs confirm the findings from chickens. The first documented case of a child acquiring resistance to an antibiotic from cattle in the US was reported in 2000. (116)

Europe banned the use antibiotics as feed additives of those antibiotics that were used in humans (117). However, there is no such ban in the United States. Past legal attempts to alter regulation have not been successful (118). It appears that the regulatory climate is beginning to recognize antibiotic resistance as a serious problem. Recently, the FDA has proposed that two antibiotics used in chicken feed be withdrawn from use (119). In another related issue, the FDA has also proposed modifications of labeling requirements for antibiotic use in humans to deal with the problem of antibiotic resistance. (120). These changes propose to amend the pertinent sections of the regulations (21 CFR part 201) to include reminders to physicians for proper use of antibiotics (e.g., proven bacterial infection and the type of organism involved along with its susceptibility, use of narrow spectrum rather than broad spectrum) and patient education. Surprisingly, the suggested changes do not include the role of pharmacists in combating this problem. They can be a valuable source for physicians and patients with respect to prudent antibiotic use. A second weakness of the proposed changes is that it does not include all antibiotics. Antibiotics used to treat mycobacterial infections (e.g. rifampin and clarithromycin) were exempted without providing any reasons for such exclusion. These issues have been brought to the attention of the FDA (121). It is hoped that the final rule expected later in 2001 would incorporate these suggestions. The steps taken by the FDA in control antibiotic use in animal fed and antibiotic use in humans are steps in the right decision to solve a potentially serious public health problem (122).

Use of Police Powers of the State to Combat Antibiotic Resistance

The coercive powers of the state are needed to maintain public health. Coercion can be defined as the "act of compelling someone to do something by the use of power, intimidation, or threats" (123). This has been true since the early Roman and Venetian times public health (124). Sanitation laws can be found in the Bible. (125) The facts surrounding the tuberculosis (TB) epidemic in New York City and the actions taken by public health officials in that city to combat the problem serve as a model to treat the growing problem of antibiotic resistance in the United Sates and abroad. Fear of an epidemic of multidrug-resistant TB was what prompted health officials of New York City to act. Tuberculosis incidence rates increased steadily between 1980 and 1989 and almost doubled from 19.9 to 36 per 100,000 populations during this decade(126). The increase was even more dramatic in certain parts of New York City, such as Harlem where TB incidence rates were about 5 times higher. By 1990, the situation had reached crisis proportions. New York City with 3 % of the nations population accounted for 15% of TB cases. The most troubling aspect of this high incidence was that about 50% of the multi-drug resistant tuberculosis (MBRTB) cases were found in New York City! A combination of `healthcare failures, social transformation and social factors was responsible for this appalling situation. (127)

There were warning signs that the City had a serious TB problem for a long time. However it was only in the late 1980s that public health officials moved to take action. In 1988, the Chief of Infectious Diseases said "because the surveillance system had broken down, and the system was inadequately funded, there was no knowledge of the size of the problem in the first place never mind a plan of what to do" (128). Failure of the TB infected individual to ingest his or her medication was one of causes of this dramatic increase in MDRTB. Many issues relating to the dynamics of transmission of the infection are not fully understood. It is beyond the scope of this article to go into the details of this transmission. The focus will instead be on issues relating to development of MDRTB. Random genetic mutation is one mechanism by which a pathogen such as Mycobacterium tuberculosis, the bacteria that causes TB, develops resistance to antibiotics. It has been estimated that this spontaneous mutation occurs in 1 in every million to 10 million replications (129). Since mutations are caused by independent chromosomal changes, development of resistance to two drugs is further decreased to 1 in 100 billion replications. Therefore, the probability of developing MDRTB increases in patients who do not take all the prescribed mediations. In NYC, TB mostly afflicted the homeless, alcoholic, drug addicts and the HIV infected. According to one source, this population does not have the incentive to adhering to drug treatment or seek treatment (130). Therefore, it was decided to implement directly observed therapy (DOT), where a patient takes his medication under the supervision of a health worker; DOT has had great success in reducing MDRTB in the New York City area.

As indicted, uncontrolled use of antibiotic can result in serious health risk to the citizens of a state. Therefore, using its police powers, a state can control/regulate the use of antibiotics as a public health and safety issue, as long that regulation is "rationally related to legitimate public purpose of public safety and health" (131)

. Detention of infected patients who the courts have upheld pose risks to public health provided constitutional issues such as due process are respected. (132) . Such rules should become applicable to persons who are known to harbor dangerous bacteria that are resistant to most present day antibiotics.

CONCLUSION

In conclusion, antibiotic resistance is a multi-faceted international problem. Therefore, a successful program to combat antibiotic resistance will require collaboration between governments at the local, national and international governments, including financial support and harmonization of public health and antibiotic usage laws. Education of patients and health care professionals, especially physicians and pharmacists, regarding the dangers of antibiotic resistance is also critical to the success of this program. The challenge is to develop a program that seeks to balance

co-operation of patients and health providers with regulatory enforcement of antibiotic use across the globe.

1. RJ Coker. From Chaos to Coercion (2000) at 141

2. MMWR 28, 1999; 1999 WL 103739084

3. U.S. Congress Office of Technology Assessment. Impacts of Antibiotic Resistant Bacteria 1 (1995**)**

4. J. Travis, Reviving the Antibiotic Miracle? 264 Science 361 (1994) (Laboratory experiments have shown that Staphylococcus ("Staph") infections can become resistant to vancomycin treatment, having acquired such abilities from Enterococcus. Since vancomycin is the last line of defense against "Staph" infections, the seriousness of the therapeutic problem is obvious. Though not yet detected clinically, a strong possibility exists that vancomycin resistant "Staph" infection could become infectious disease nightmare

5. See FN 3

6. A. Tomasz. 330 New England J. Medicine 1247 (1994) (This report form a workshop held at the Rockefeller University has startling statistics that should not be ignored: (a) There has been a surgence of bacterial and viral disease since 1990s (b) About 60000-70000 patients dies of nosocomial infections every year in the United States (c) About 40% (total cases: 1900) patients with vancomycin-resistant blood stream infections died of the infection (d) Federal amount spent on monitoring resistance to anti-bacterial and anti-virals is a miniscule $48,795.

7. RW Pennir et al: Trends in Infectious Disease Mortality in the United States, 275, JAMA 189 (1996).

8. LN Horvitz, It's a war to Restore Antibiotics, Insight on the News, Mar. 18, 1996 at 38 (quoting M. Misocky, 30 Akron L. Rev, FN 63)

9. PD Fey, TJ Safranek, MR Rupp Et Al. Ceftriaxone-resistant Salmonella Infection Acquired by a Child from Cattle, 342 New Eng J Med 1242-1249 (2000) (ref 1,2)

10. PS Mead, L Slutsker, V. Dietz et al. Food-related illness and death in the United States. 5 Emerg Infect Dis. 607-625 (1999).

11. Sepsis is a condition when the immune system, designed to fight pathogenic bacteria, starts to attack damages the body (e.g. sepis can make blood-vessels leaky so as to cause life-threatening drops in blood pressure and organ failure). When the immune system has successfully fought off the invading bacteria, it receives a "victory" signal to end the defensive action. This cutoff mechanism fails usually in patients with compromised immune systems such as AIDS patients.

12. See R. Stone. Search for Sepsis Drugs Goes On Despite Past Failures. 264 Science at 365

13. SD Holmberg et al 9 Rev Infect Dis 1065 (1987) (quoting FN 16, ref. 5)

14. L. Garrett The Coming Plague (1994) at 414.

15. Crosby AW Jr. Epidemic and peace, 1918. Westport, Connecticut: Greenwood Press, 1976: 311

16. United Nations Program on HIV/Aids and World Health t Organization. AIDS epidemic update: December 1998. Geneva, Switzerland: World Heath Organization, 1999 (http://www.unaids.org/highband/document/edidemio/waqrr98e.pdf)

17. SV Johnson. 15 Pharmacotherapy 579 (1995) (Inappropriate Vancomycin Prescribing based on Criteria from the Centers of Disease Control)

18. 59 Federal Register 25758, (1994)

19. Id.

20. Id

21. See FN17

22. HICPCC, 16 Infection Control Hosp. Epidemiol. 105 (1995)

23. See FN 16 supra

24. http://www.healthsci.tufts.edu/apua/News/news.html. Details of this bill (H.R. 1771), entitled "Antibiotic Resistance Prevention Act of 2001" which is first of its kind and was introduced in the House of Representatives by Mr. Sherrod Brown (D, Ohio) in the 1st session of the 107th Congress, can be found at this web site

25. Id

26. GJ Totora, BR Funke and C. Case. Microbiology- An Introduction. 5th Edn. (1995) at 71. (This book also has a section that helps with pronunciation of bacterial names)

27. SB Levy. The Antibiotic Paradox at 19 (Levy from now)

28. Id at 31

29. Id at 74

30. Id at 72 (a single mutation takes place in every 10 to 100 million divisions)

31. Id at 72 (it was calculated that for a bacteria to become resistant to 4 antibiotics by mutation alone would take an astronomical and impossible time of about a trillion trillion (~ 1024 years).

32. Levy at 300

33. Levy at 78

34. Plasmid is defined as "[a] small cyclic DNA replicating independently of the chromosome" (Levy at 69)

35. http://www.healthsci.tufts.edu/apua/News/news.html. (H. Westh: Influence of erythromycin consumption on erythromycin resistance in Staphylococcus aureus in Denmark. 13 APUA Newsletter at 1-4 (A resistant gene located on a plasmid (ermC) replaced the resistance gene located on the chromosome (ermA) as the predominant resisatnce gene to erythromycin.

36. Levy at 80

37. Id at 82 (Though a plasmid can enter from E. Coli to H. influenzae, it cannot survive inside the later. The transposons have other options; they can "jump" on to the chromosomes or plasmids present in H. influenzae.

38. Id at 82

39. Id at 83

40. Levy at 89

41. H. Nikaido. 264 Science 382 (1994) (Prevention of Drug Access to Bacterial Targets: Permeability Barriers and Active Flux)

42. Id at 385 (One major reason for the resistance of the bacteria P. aeruginosa to many antibiotics is to presence of an efflux system which removes these drugs when they enters the cell)

43. J. Davies. 264 Science 375 (1992). This paper contains many more examples of inactivation of antibiotics by bacteria.

44. Id

45. BG Spratt. 264 Science 388 (1994)

46. Levy at 72

47. See generally Coker (FN 1)

48. RP Wenzel and MB Edmond. 343 New England Journal of Medicine 1961 (This paper states that 160 million antibiotic prescriptions are written each year. Of the 25 tons of antibiotics 50% are used in humans and the other 50% are used in animals (including fish) and agriculture.

49. R. Gasbarro, Combating Growing Bacterial Antibiotic Resistance, American Druggist, Feb. 1996 at 49

50. Levy at 53

51. Id at 51 (Table 1). Physician acquiescence is most likely to maintain patient loyalty and to benefit patient

52. SB Levy Scientific American (1998, March) at 46 (or at

http://www.sciame.com/1998/0398issue/0398levy.html)

53. Griffith v. West Suburban Hospital (case No. L-23904, Cook County, Illinois Circuit Court 1993 (quoting FN 3 at 76)

54. Inflammation of the heart

55. Orbay v. Castellanos (Case No. 91-36124, Dade County Circuit Court, Miami, Florida, 1993 (quoting FN 3 at 75)

56. SB Levy Scientific American (1998 March at 46 (The Challenge of Scientific Resistance)

57. SZ Hirschman et al. Use of Antimicrobial Agents in a Teaching Hospital, 148 Archives of Internal Med. 2001 (1988)

58. Id

59. M.T. Osterholm et al Principles and Practice of Infectious diseases, GL Mandell, JE Bennett, R. Dolin (Eds, 1999? (FN 4 Berkelman, Sci. 1994)

60. RL Berkelman et al 264 Science 368 (1994)

61. Id.

62. A. Novitt-Moreno, Antibiotics: What's happening to our Miracle Drugs? CURRENT HEALTH, Dec. 1995, at 6. "It takes about 14 years and almost 400 million dollars to develop a new antibiotic.."

63. Levy at 53

64. See generally OHIO REV CODE Ann. Drug Laws of Ohio (Banks-Baldwin 1996)

65. Sickling v. State Medical Bd., 575 N.E.2d 881, 883 ((Ohio App, 1991) (holding that a physician's license be revoked for violating Ohio Rev Code Ann. 4731.22B, which sates in part:" Failure to use reasonable care discrimination in the administration of drugs, failure to employ acceptable scientific method in the selection of drugs Â… in the treatment of disease."

66. Gingo v. State Medical Board 564 N.E. 2d 1096 (Ohio App. 1989) (the court held that "Dr. Gingo's weight loss 'system' is precisely the opposite of what one would expect to find in a program purported to enhance overall good health. In truth, his proposed solution to an admittedly significant problem- obesity- ultimately promotes a far more alarming epidemic: drug misuse . . ." Id at 1099.

67. See FN 64

68. 21 USC sec 891 et seq

69. 0 21 USC sec 812 (b) (Schedule I classification includes drugs that have a high abuse potential or no therapeutic use in treatment in the United States, or is unsafe even under medical supervision

Schedule II includes those drugs that, though they have high potential for abuse, are currently accepted for medical use in the United States with severe restrictions. Schedule III are those drugs with a lesser potential for use that drugs in Schedule II,

and I and are accepted for medical use. (4) Schedule IV drugs r have a lower potential abuse and psychological dependence than those in Schedule III and medically accepted for use. (5) Schedule V classification includes those drugs lower potential for abuse and psychological dependence than those in Schedule IV and are medically accepted.

70. PB Hutt and RA Merrill. Food and Drug Law 2nd Edn. (1991) at 536

71. SB Markow. 87 Geo.L.J. 531

72. Id at 542

73. Markow,

74. See Part III

75. http://www.healthsci.tufts.edu/apua/News/news.html. Linezolid is a new antibiotic which is a structurally different antibiotic introduced in the last 3 decades. Five Patients have been reported to be resistant to this novel antibiotic. These patients received the drug over 3 to 6 weeks, once again demonstrating that development of resistance is a strong possibility when a single antibiotic is used over long periods.

76. Markow, FN 115

77. See FN 24

78. See FN5 at 1247 (Methicillin-resistant Staphylococcus aureus increased 5-fold (from 8 to 40%) in clinical samples between 1986 and 1992.obtained from a large teaching hospital)

79. 42 CFR 405.1022 (c)

80. Id

81. 48 FR 299

82. Markow page 21 (FN 81)

83. 51 FR 22027

84. see FN 36

85. The composition of the infection committee is critical. Therefore, one modification will require that all members have expertise in ate area of infectious diseases. The second modification to the committee membership is that it includes pharmacists with specialization in infectious disease. Pharmacy education has become more clinically and drug-use oriented in the last 2 decades with opportunities to specialize in infectious diseases.

86. 21 CFR § 314.80 (a)

87. Id

88. Pub. L. No. 75-717, 52 Stat 1040 (1938) as amended; 21 USC §§ 301 et seq

89. Antibiotics come under the definition of a drug as defined in § 201(g) of the FDCA.

90. "No person shall introduce or deliver for introduction into interstate commerce of any new drug, unless approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug" 21 F USC § 355

91. 21 CFR § 312.23(a)(8) (1997)

92. Outside the living body and in an artificial environment, Webster's Collegiate Dictionary, 10th Edn

93. 21 CFR 312.21

94. 21 USC § 355 k

95. PB Hutt, RA Merrill. Food and Drug Law - Cases and Materials .2d Edn. (1991) at 537.

96. 21 USC sec 371(a)

97. New drug, Antibiotic and Biological Drug Product Regulations; Accelerated Approval 57 Fed. Reg. 58942 (1992)

98. Id

99. See Marion J. Finkel, Phase IV testing: FDA Viewpoint and Expectations, 33 Food Drug Cosm. L.J. 181 (1978)

100. 21 CFR§ 310.305(b) (An ADE has been defined as "any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug over dose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse drug event occurring from withdrawal and any failure of expected pharmacological action"

101. Id

102. Id (Life-threatening ADE is defined as: "Any {ADE] that places the patient, in view of the initial reporter, at immediate risk of death from the [ADE] as it occurred; i.e., it does not include an [ADE] that, had it occurred in a more severe form, might have caused death"; Serious ADE is defined as" Any [ADE] occurring at any dose that results in any of the following outcomes: Death, life-threatening [ADE], inpatient hospitalization or prolongation of existing hospitalization, a persistent or significance disability/incapacity or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious [ADE] when based on appropriate medical judgment, they may jeopardize they patient of subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at a home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Unexpected ADE is defined as "any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and path physiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of grater severity) if the labeling only referred to elevated enzymes of hepatitis. Dimi9larly, thromboembolism, and cerebral vascular vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents." Unexpected' as used in this definition, refers to an [ADE] that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product."

103. 21 CFR § 310.305(c)(1)(i) (These are called "post-marketing 15-day 'Alert reports")

104. 21 CFR § 310.305(d) (1)

105. http://www.fda.gov/medwatch/report/instruc.htm

106. 21 CFR § 310.305(c)(2) (Each person . . .shall promptly investigate all serious, unexpected adverse drug experiencers that are subject to post marketing 15-day Alert reports and shall submit follow up reports within 15 calendar days of receipt of new information or as requested by the FDA ")

107. Id

108. 21 USC § 310.355 (k) (1) ("In the case of any drug for which an approval . . . is in effect, the applicant shall establish and maintain such records and make such reports to the Secretary, of data relating to clinical experiences and other data or information . . .with respect to such drug; 21 USC 701(a) (the authority to promulgate regulations for the efficient enforcement of {FDCA, . . . is vested in the Secretary)

109. http://www.fda.gov/medwatch/report/instruc.htm

110. Levy at 137

111. Id

112. Id

113. Levy at 140

114. Levy at 145

115. Levy at 147

116. PD Fey, TJ Safranek, MR Rupp et al. Ceftriaxone-resistant Salmonella Infection Acquired by a Child from Cattle, 342 New England J Med 1242-1249 (Samples obtained from a 12-year old child, with acute abdominal pain and fever, contained the identical type of resistance found in samples obtained from cattle.

117. Levy at 241

118. Id. (The National Resources Defense Council sought to have the FDA deal with this problem by filing an "Imminent Hazard" petition in 1985. It was rejected by then Secretary of Health and Human Services Margaret Heckler. However, this problem was studied by the prestigious Institute of Medicine of the National Academy of Sciences which concluded that it was "unable to find a substantial body of direct evidence that established the existence of a definite human health hazard

119. http://www.healthsci.tufts.edu/apua/News Articles/Poultry-Wi (The cause of a specific type of resistance in humans (fluoroquinolone-resistant Campylobacter) is caused by eating chicken treated with these antibiotics.

120. 65 FR 56511 (September 19, 2000)

121. http://www.healthsci.tufts.edu/apua/News Articles/Poultry-Wi

122. Id (The infectious Diseases Society of America supports the FDA proposal)

123. Coker, at 17

124. EPRichards. Public Health law

125. Id (citing Leviticus 11-17)

126. Coker at 48

127. Coker, at 55

128. Coker at 84

129. Coker at 145

130. Coker at 151

131. 0 New York City Friends of Ferrets v. The City of New York, 876 F.Supp. 529 (City ordinance prohibiting keeping ferrets as pets within city limits was challenged based on equal protection rights of ferret owners was upheld by the court since it was rationally related to legitimate public health purpose of public health and safety

132. Gastin Maryland Law Review 1995 at 1 [(quoting DP Fidler 4 Emerging Infectious Diseases, FN 42) (1998)