Microbiological Products and Regulation: An Overview

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Abstract— The term industrial microbiology refers to the use of microorganisms for industrial purposes. Such things as anticoagulants, antidepressants, vasodilators, herbicides, insecticides, plant hormones, enzymes, and vitamins have been isolated from microorganisms or produced in large quantities by genetically engineering the organisms with foreign genes. Such illnesses as tuberculosis, salmonella, syphilis and some forms of meningitis are caused by bacteria. Some bacteria are not harmful, while others are good for us.

Before bacteria can multiply and cause symptoms our immune system can usually destroy them. We have special white blood cells that attack harmful bacteria. Even if symptoms do occur, our immune system can usually cope and fight off the infection. There are occasions, however, when it is all too much and our bodies need some help - from antibiotics.

Index Terms— Microbiological products, antibiotics, vaccines, probiotics, etc.

I. INTRODUCTION

The term industrial microbiology refers to the use of microorganisms for industrial purposes. Such things as anticoagulants, antidepressants, vasodilators, herbicides, insecticides, plant hormones, enzymes, and vitamins have been isolated from microorganisms or produced in large quantities by genetically engineering the organisms with foreign genes.

Microbiological products are antibiotics, vaccines, probiotics, etc

1) Antibiotics: anti-meaning 'against' and bios meaning 'life' (a bacterium is a life form).' Antibiotics are also known as antibacterial, and they are drugs used to treat infections caused by bacteria. Bacteria are tiny organisms that can sometimes cause illness to humans and animals. The singular word for bacteria is bacterium.

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   Before bacteria can multiply and cause symptoms our immune system can usually destroy them. We have special white blood cells that attack harmful bacteria. Even if symptoms do occur, our immune system can usually cope and fight off the infection. There are occasions, however, when it is all too much and our bodies need some help - from antibiotics.
2) Vaccines: A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

Probiotics: Probiotics are live microorganisms thought to be beneficial to the host organism. According to the currently adopted definition by FAO/WHO, probiotics are: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host". Lactic acid bacteria (LAB) and bifidobacteria are the most common types of microbes used as probiotics; but certain yeasts and bacilli may also be used. Probiotics are commonly consumed as part of fermented foods with specially added active live cultures; such as in yogurt, soy yogurt, or as dietary supplements

II. REGULATIONS

- Antibiotic: FDA's Approach to Antibiotic Regulation

Controversy has simmered around the use of antibiotics in food animals for over three decades. Recently, the debate has heated up—increasingly strong evidence is emerging that the practice of giving livestock antibiotics is making some human illnesses once again untreatable, as bacteria which cause the illnesses become resistant to the antibiotics used to treat them.

Under the Food, Drug, and Cosmetic Act, the Food and Drug Administration (FDA) has the authority to restrict the use of antibiotics in animals based upon the potential risk to human health. Historically, concerns about human safety with new agricultural antibiotics focused primarily on ensuring that drug residues in food were safe for human consumption. Now, the FDA plans to extend authority to cover the indirect risks to human health caused by the loss of drugs due to resistance.

Beginning in 1998, the FDA began to restructure its drug-approval system for food-producing animals. In November of that year, the FDA published new guidance, "Guidance for Industry # 78", which spelled out the FDA s intent to take the indirect human health effects of antibiotic resistance into account in the drug-approval process. Later, in January of 1999, the FDA took a second step, releasing the so-called "Framework" document. This draft report outlined the FDA's approach for registering new antibiotics intended for food animals. This risk-based approach attempts to balance the protection of human health against the benefits of antibiotic use in livestock operations.

The FDA's approach is complicated and data intensive. The draft Framework sets out a complex scheme for evaluating and then minimizing adverse human health effects of new animal drugs. New antibiotics first would be categorized by their importance in human medicine and by their proposed use—to determine the potential for human exposure to drug-resistant bacteria if drug-resistance develops from the use of a new antibiotic. This categorization would be used to determine the extent of monitoring programs before and after a new drug is approved for use in food animals by the FDA.

- Evaluation of Potential Risk

The FDA's approach categorizes new drugs based upon their importance in human medicine and on the likelihood of human exposure to resistant bacteria. A drug's importance in human medicine would place it in one of three categories. Category I covers drugs essential for treating serious or life-threatening diseases in humans, while Category II covers drugs of choice in the treatment of potentially serious diseases, but for which alternative treatments exist. Category III includes drugs that have little or no use in human medicine. Additionally, the FDA considers that any antibiotic which causes cross-resistance to a drug within one of the three categories, to also be included in that category.

The second part of this evaluation - the ranking of the potential exposure of humans to resistant bacteria, either directly or indirectly - is a more difficult task. The approach considers such factors as a drug s attributes (e.g., mechanisms by which a bacterium develops resistance to that drug), product use (e.g., dose or duration of treatment), and potential human contact (e.g., animal management practices) when categorizing the likelihood of human exposure. Based upon the results of this review, a drug would receive a high, medium, or low classification.

The combined results of these two classification schemes would determine which new drugs would require pre-approval studies and post-approval monitoring.

Pre-approval Studies: Predicting Resistance Problems
The FDA's Framework envisions requiring pre-approval studies only for those antibiotics that appear likely to pose high public health risks on the basis of the classification scheme. Pre-approval studies would provide information about what might happen once a new antibiotic is in use. They would attempt to determine the likelihood of bacteria developing resistance and what changes might be expected to the mix of bacteria in the animal s intestine. With this information, the FDA would try to develop post-approval studies.

The FDA strategy for predicting resistance considers both the quantity of bacteria that could make people will present in the animal at the time of slaughter (i.e., what is termed the pathogen load) and the number of types of bacteria present in the animal that are drug-resistant (prevalence of resistance).

- Pathogen Load:

Generally, antibiotics are given to reduce the quantity of a target bacteria. However, the antibiotic may also disturb the normal balance of bacteria in an animal s stomach. For example, an antibiotic may make an animal well by decreasing the class of bacteria causing its illness, but may at the same time increase a type of bacteria that can infect people a human pathogen. Animals carrying large amounts of a human pathogen at the time of slaughter could increase the risk of human illness.

- Prevalence of Resistance:

The greatest danger occurs if the human pathogens are resistant to antibiotics. When assessing prevalence of resistance, the FDA would want information in both human pathogens and nonpathogenic bacteria. Antibiotic resistance can develop in bacteria that do not cause human illness and, in some circumstances; these nonpathogenic bacteria may transfer their genes for drug resistance to bacteria that cause human diseases.

- Post-approval Studies

The Framework calls for the post-approval monitoring of new drugs in hopes of being able to take action before the threat to human health develops. After a new antibiotic was approved for use in food animals, the FDA would set both resistant and monitoring thresholds as part of an early warning system for detecting and evaluating resistance development. A resistance threshold is a defined level of drug resistance that a bacterial population could develop before the risk to human health was seen as significant. The monitoring threshold would be the level of antibiotic resistance in a particular bacterium at which the FDA would begin steps to address the development of drug resistance.

Ideally, the FDA would detect resistance development, study its causes, and provide strategies to mitigate resistance development. If researchers could not find alternatives to retard the development of resistance, the Framework envisions withdrawal of a drug from the marketplace. The Framework acknowledges the difficulty of establishing and detecting scientifically based resistance and monitoring thresholds. It also acknowledges that without reliable thresholds, the FDA may not be able to approve new uses of antibiotics.

- Existing Drug Approvals

The Framework focuses almost exclusively on the evaluation and approval of new antibiotics, giving scant attention to the review of previously registered drugs. The only reference toward addressing resistance development in existing drugs is a footnote stating that the framework, if finalized and implemented, would also be used for reviewing these antibiotics as resources permit.

III. VACCINES

- Regulation of vaccines

Regulatory issues related to a particular candidate vaccine should be considered early in the development process, since compliance with regulatory requirements is the basis for eventual approval. It is strongly recommended that dialogue with the appropriate national regulatory authority be established early on. The national regulatory authority should review the plans for development of the candidate vaccine and clarify requirements for carrying out clinical trials, as well as for marketing approval.

The regulation of vaccines can be divided into three stages: developmental, licensure and postlicensure. The developmental stage consists of two parts, preclinical research and development, and clinical research and development.

- Preclinical testing

Preclinical research and development are carried out in the laboratory using in vitro techniques or, when necessary, in vivo techniques in animals. The data from preclinical and laboratory research include details of the development and production of a vaccine together with reports of control testing, which should be adequate to justify subsequent clinical studies in humans.

- Phases of clinical development (I–III)

Clinical trials in humans are classified into three phases: phase I, phase II and phase III and in certain countries formal regulatory approval is required to undertake any of these studies. This approval takes different forms in different countries (e.g. Investigational New Drug Application (IND) in the United States and Clinical Trial Certificate or Clinical Trial Exemption (CTX) in the United Kingdom).

The phase I clinical studies carry out initial testing of a vaccine in small numbers (e.g. 20) of healthy adults, to test the properties of a vaccine, its tolerability, and, if appropriate, clinical laboratory and pharmacological parameters. Phase I studies are primarily concerned with safety. Phase II studies involve larger numbers of subjects and are intended to provide preliminary information about a vaccine's ability to produce its desired effect (usually immunogenicity) in the target population and its general safety. To fully assess the protective efficacy and safety of a vaccine, extensive phase III trials are required.

The phase III clinical trial is the pivotal study on which the decision on whether to grant the licence is based and sufficient data have to be obtained to demonstrate that a new product is safe and effective for the purpose intended.

By the beginning of the phase III stage of development, a vaccine should have been fully characterized and the final manufacturing process, specifications and batch release testing procedures should have been established. An application for market authorization may be submitted to an NRA on the basis of the data from phase III testing and if approved, the vaccine then becomes commercially available in that particular country. If a product contains or consists of genetically modified organisms an environmental risk assessment should also be undertaken and approved by the appropriate agency.

The structure of the clinical development programme must be tailored to the type of vaccine and the antigenic content. For example, the clinical evaluation of a vaccine that contains only novel antigen(s) may of necessity be very different from that of a vaccine that contains one or more previously evaluated antigens. Such factors also influence whether clinical protection trials will be required, whether or not they are feasible, or whether an approval may reasonably be based on immunogenicity data. In all instances, it is the obligation of the applicant to justify the content and structure of the clinical development programme. Pre-submission meetings with regulatory authorities may assist in ensuring that the content of the final data package is likely to be acceptable.

- Issues to be considered after the initial licensure

In addition to phase I, II and III studies that may be performed before or after the first licensure of a new vaccine, which are described under other relevant trials as outlined above, the post marketing period is critical for the collection of data on the safety and effectiveness of a vaccine in large numbers of recipients; these data may come from both active and passive modes of surveillance. Following licensing, there is continued surveillance of vaccines for adverse events, especially for those rare events that can be detected only in very large numbers of subjects.

Any change in production methods or scale-up following licensing will necessitate further product characterizations to demonstrate equivalence, although the extent of re-characterization required depends on the nature of the changes implemented. Further characterizations should be documented and the NRA should be notified of all changes. Regulatory authorities should clearly define and implement in their regulations which changes require only a notification and which changes require a formal approval before they can be introduced.

This will be decided on a case-by-case basis and, in all instances, regulatory approval for a change must be obtained before the vaccine is used.

IV. PROBIOTICS

Evaluation of safety of probiotics for human use:

In recognition of the importance of assuring safety, even among group of bacteria that are Generally Recognized as Safe (GRAS)**, probiotics strains needs to be characterized at a minimum with the following tests:

- Determination of antibiotic resistance patterns. It should be ascertained that any given probiotic strain is not at significant risk with regard to transferable antibiotic resistance.
- Assessment of undesirable side-effects.
- If the strain under evaluation belongs to a species that is a known mammalian toxin producer or of hemolytic potential, it must be tested for toxin production and hemolytic activity respectively.

Assessment of lack of infectivity by a probiotics strain in immunocompromised individuals would be an added measure.

Evaluation of efficacy studies in humans:
The principal outcome of efficacy studies on probiotics should be proven with similar benefits in human trials, such as statistically and clinically significant improvement in condition, symptoms, signs, well-being or quality of life, reduced risk of disease or longer time to next occurrence or faster recovery from illness. Each of the parameter should have proven correlation with the probiotics tested.

Probiotics delivered in food may not be tested in Phase 3 studies (effectiveness), unless the product makes a specific health claim wherein it becomes imperative to generate the required evidence necessitating carrying out Phase 3 studies.

If a probiotic food has a record of documented long and safe use outside the country, the data regarding this could be reviewed and deemed as sufficient to allow its marketing within the country. However, labeling of health benefits may require evaluation in a different manner. While taking into account studies done abroad, efficacy studies of probiotics (which are of proven benefit in ‘other’ populations) should also be conducted on Indian subjects. It is recommended that such ‘bridging’ human trials should comply with the principles laid down by the Drug Regulatory Authority. Adverse effects, if any, should be monitored and incidents reported to the appropriate authority.

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