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Andrology Lab Corner

A Short Course on the Food and Drug Administration: What You Should Know

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US government bureaucracy and regulatory agencies are thought of as pits of deep mystery to most scientists, but the regulatory issues are built on codes and precedent. The Food and Drug Administration (FDA), or "the Agency", has the responsibility for ensuring the safety and efficacy of all regulated marketed medical products including drugs, biologics, medical and radiation-emitting devices, and special nutritional products and is charged with ensuring the safety of products for the consumer. A basic understanding of the Agency and the rules it lives by can be gained by learning how to access information at the FDA Web site (http://www.fda.gov). Whether it be a drug, a device, a diagnostic test, or even a cosmetic, the FDA Web site offers a wealth of information to match the creativity of the andrology community. The clinical lab andrologist can use the Web to understand the approval or clearance process of the laboratory products it uses.

Structure of the FDA

Prior to FDA oversight in 1906, quackery medicines, nostrums, and alcohol ruled (Sinclair, 1906). Over the years, the manufacturing and safety of products took precedence in the FDA until 1962, when efficacy became important after the thalidomide disaster. The growth of the Agency has kept pace with changes in regulatory authority to protect the consumer. Today, the Agency consists of 6 centers regulating the safety and efficacy of products across a wide spectrum. Four of these 6 centers are important to most andrologists; these are the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), and the Center for Food Safety and Applied Nutrition (CFSAN). For example, the scope of devices and diagnostic tests was encompassed by the 1976 Medical Device Amendments—and resulted in the formation of the CDRH. The Code of Federal Regulations (CFR) for each "Center" is available on the Web (http://www.access.gpo.gov/nara/cfr/) and is the basis for the regulatory authority for each Center. The andrologist involved in assisted reproductive technology (ART) interacts with the regulatory authority of several of these centers. I will use examples from

several of these centers to demonstrate how you can access information.

The drugs used to stimulate ovulation are approved through the Division of Reproductive and Urologic Drug Products (DRUDP) of CDER. Drug products used in ART include gonadotropin agonists, antagonists, and recombinant follicle-stimulating hormone. The purpose of these products is to stimulate the ovary, and their approval was based on appropriate preclinical, manufacturing, safety, and efficacy data submitted to the agency as a new drug application (FDA guidance paper 3, http://www.fda.gov/cder/guidance; FDA Consumer, 1995). One can explore the FDA/CDER Web sites, look for announcements of recent approvals, and ask to be put on the e-mail list. The final label included with the product and advertisements are based on the scientific data supporting the approval of the drugs. The label is reproduced in the Physician's Desk Reference if the manufacturer is willing to pay page charges.

The pipettes, needles, and catheters used in ART are cleared through the Obstetrics and Gynecology Devices Branch in the Division of Abdominal, Reproductive, and Ear, Nose, and Throat (ENT) Devices at the CDRH. Devices that are labeled for assisted reproduction must first obtain premarket clearance (FDA guidance paper 1). A second important CDRH group is the Division of Clinical Laboratory Devices (DCLD; FDA guidance paper 2; Gutman et al, 1998). For example, the andrology community remembers well the first Computer-Aided Sperm Analysis (CASA) systems given premarket approval (PMA) by the DCLD. Semen counters, sperm integrity, prostate-specific antigen assays (PSA), and pregnancy tests are all in vitro diagnostic (IVD) tests reviewed by the DCLD. IVD products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae (section 201(h) of the Federal Food, Drug, and Cosmetic Act [FD&C Act]; CFR 809.3). Since CDRH was not present prior to 1976, it should be no surprise that if a device was available prior to 1976, it needs no clearance. However, if new claims, indications, or intended uses are required, data must be provided for those claims. The key to knowing what needs to be submitted depends on whether you plan to market and advertise the product. The Medical Device Amendments of 1976 to the FD&C Act established 3 regulatory classes for medical devices on the basis of the degree of control necessary to ensure that the various types of device are safe and effective (CFR 21-809.3). The 3 categories are as follows: class I (low risk), class II (moderate risk), and class III (high risk) products. Class I products are largely exempt or occasionally reviewed as 510 (k)s, class II products are subject to 510(k) review, and class III products are usually subject to PMA review, which is, in effect, a license granted to the applicant for marketing a particular medical device after review of the clinical studies.

Even CBER plays an important role in the life of the andrology lab. CBER is usually thought of as the vaccine and blood products Center, but on July 6, 2001, CBER advised the community that it had jurisdiction over human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei, including the transfer of ooplasm that contains mitochondrial genetic material and genetic material contained in a genetic vector, transferred into gametes or other cells (FDA Letter to Sponsors/Researchers, 2001). Recently, the Biological Response Modifiers Advisory Committee (Division of Therapeutic Proteins) discussed issues related to ooplasm transfer in assisted reproduction specifically directed to the topics of mitochondrial transfer with ooplasm transfer at the time of in vitro fertilization. The FDA-advertised advisory meetings give a glimpse of the risk-benefit, safety-efficacy issues that confound each day at the regulatory agencies. The entire transcript of this and other meetings can be found on the Web (FDA transcripts, 2002).

The CFSAN provides a glimpse into products that have minimal regulatory oversight. By law, the FDA does not have the authority to approve cosmetic products or ingredients, except for color additives.

Regulations do prohibit or restrict the use of several ingredients because of safety concerns and require that the product carry the following warning on the label: "Warning: the safety of this product has not been determined" (http://www.cfsan.fda.gov/; FDA Consumer, 1995). With the exception of colors and certain prohibited ingredients, a cosmetic manufacturer may use essentially any raw material in a product and market it without prior FDA approval. The yin-yang of regulatory authority is the yin-yang of politics; in other words, while Congress intends to safeguard the health and economic interests of consumers, it also means to protect a manufacturer's right to market a product free of excessive government regulation. Registration and reporting of cosmetics is essentially voluntary. Although cosmetic claims, even those considered "puffery", are allowed without scientific substantiation, if a cosmetic makes a medical claim, such as removing dandruff, the product is regulated as an over-the-counter drug for which scientific studies demonstrating safety and effectiveness must be submitted to the FDA. Federal regulations require ingredients to be listed on product labels in descending order by quantity. Because cosmetic ingredients are often complex chemical substances, the list may be incomprehensible to the product's average user (FDA Consumer, 1991). However, if all manufacturers use the same name, consumers can compare different products and make reasonable value judgments.

The passage of the Dietary Supplement Health and Education Act (DSHEA) of 1994 limits manufacturing and regulatory oversight (DSHEA, 1994). The advertisements of dietary supplements are rich with promise, but the quality of many is suspect. Contaminants have been identified in them, and all athletes are well-advised to stay away from these over-the-counter supplements for their own safety (Catlin et al, 2000; USADA resource papers, http://www.usantidoping.org). The most well-known dietary supplement is androstenedione, one of at least 8 androgenic substances that are marketed over the counter. This precursor of both estrogens and androgens was first abused by the East German Olympic athletes in the 1970s to improve performances and was banned by the International Olympic Committee in 1997. It is the same compound to which Mark McGwire attributed his success.

Summary

It is important for a laboratory scientist to understand the regulatory pathway for the products in daily use. In addition, many of you will also be interested in identifying and marketing new drugs, devices, and cosmetics and will benefit from understanding fully the CFR and various guidance papers available on the Web as well as understanding issues of patenting, publishing, and advertising. Fortunately, today, much of this information is easily accessible electronically. Start with http://www.fda.gov.

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