DEALING WITH ONCOLOGY DATA IN

DRUG LABELING AND BEYOND

STATEMENT OF

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I.

As an ultimate pragmatist, I believe that we need to develop a system that makes available all information about oncology drug products either in the labeling of the drug products or other publicly accessible documents that provide ratings of drug products, such as the Food and Drug Administration's (FDA's) Orange Book. Clinicians, patients, their families and friends, insurance companies, and other providers are being exposed to a cacophony of information about oncology drug products. This noise comes from variable sources, is of disparate quality, and may be unvetted. We need to consider a rating system that clarifies the quality and quantity of the data. Such an approach could be communicated clearly and concisely to interested parties. It could create an incentive for additional research, and it could be used to support reimbursement and such an approach is consistent with the historic approaches to FDA's regulation of information, especially as that authority is being refined by the courts.

II.

As we approach the 100th anniversary of the enactment of the original law to regulate drug labeling, the Pure Food and Drug Act of 1906, a historical perspective is useful. This ground-breaking statute provided limited regulatory authority over drugs. In relevant part, the government could only regulate the shipment of drugs whose labels were misbranded. Thus, the government had limited authority to deal with the overblown promotions of the time.

Congress did not add premarket approval authority over the labels and labeling of new drugs until the enactment of the Federal Food, Drug, and Cosmetic Act of 1938. It was not until the Drug Amendments of 1962 that FDA was provided FDA with the authority to regulate the advertising of prescription drugs. That statute also added the requirement that new drugs be proven effective by adequate and well-controlled clinical trials - a simple phrase that revolutionized drug development and regulation.

In that era commercial media were basic: radio and television networks, newspapers and national magazines, and expensive. Regulation was straight forward. We were also pre Medicare and Medicaid, pre cable television, pre computer, let alone personal computer, pre internet. Health care information of any kind was generated in limited amounts and was

accessible through limited means. Healthcare professionals and the government were accorded a deference that is almost unfathomable today.

In the early 1970's FDA through the notice and comment rulemaking process established a specific format for drug labeling and the package insert. One goal of this revision was to provide healthcare professionals and others with a standardized format for comparing information that FDA had analyzed and reached a conclusion about. Data from clinical and other trials as well as other relevant studies about new drugs were submitted to FDA, and only data that FDA deemed appropriate were included in the labeling as categorized by the agency. Thus, a controlled closed system existed in a simpler world.

III.

That simple system began to crack in the late 1970's and 1980's with the advent of the so-called Patient Package Insert which provided information directly for the patient that FDA had reviewed and approved. After that came Direct-to-Consumer advertising. Then the courts began to limit FDA's ability to regulate truthful information about drugs, holding that the agency is constrained by the rules that apply to the regulation of commercial speech.

For almost 30 years information about drugs was limited, and that information was available only through the FDA filter. For the past decade, however, that model has not been true. Formularies, public and private, are the norm; and therapeutic decisions are routinely made on the basis of economics. Economic decisions are made on the basis of data comparisons that FDA would never permit pharmaceutical competitors to make.

Today we face a truly new paradigm. Through technological advances, information of all quality and veracity is available. Data are available from chat rooms and unregulated sources from true believers and charlatans. Patients and their families have an insatiable appetite for information about their diseases. Negative data are often not published or released. The courts have recognized the rights and needs of the public to receive information. A coalescence of technologies and products subject to potentially differing legal standards (drugs, devices,

biologics) are now being used to treat these diseases. Practitioners are pressed for time to evaluate all these data. Payment for these treatments is critical to the patients, and the information must be made available in a useful manner to the payors. And most importantly, although the patients must be informed, they must also be alerted to worthless, misleading and worse data.

In the United States we have created a fabulous oncology research machine that has both public and private arms. The Cooperative Groups of the National Cancer Institute enroll approximately 35,000 patients in clinical trials. That number is about half of the patients on oncology clinical trials. The private sector enrolls the remainder. For children, it is estimated that 90% are treated in controlled clinical trials. These trials are designed to provide improvements over the existing standard of care. For adults, it is estimated that merely 3-5% of oncology patients are enrolled in such clinical trials. A Congressional report several years ago indicated that 70% on oncology drug use is off label, but much of this usage is the accepted standard of care among oncologists. We need to develop an information system that addresses the needs of the patients and practitioners within the real world of research, guidelines, and the need to encourage enrollment in controlled clinical trials that push that standards of care and cure rates ever higher.

IV.

Congress attempted to restrict the dissemination of information about off-label uses in the Food and Drug Administration Modernization Act of 1997, and the courts rejected those restrictions. But that is only one movement in the symphony of information that is available. Courts have held and believe that the world cannot be viewed only through the prism of FDA. Decisions, critical decisions, about life and death and payment are made on the basis of information or data that may have never been analyzed or critiqued by the agency. Further, I am a believer in the Buckminster Fuller adage that there is no such thing as negative information. A procedure is necessary that provides everyone with the information available in useful form so that everyone involved in the process can make thoughtful decisions on the basis of all the evidence.

A procedure is also necessary that encourages the submission of information to FDA or others for review, and such a system should provide an incentive toward enrollment in controlled clinical trials. For oncology drugs, affirmative reimbursement decisions are already made on the basis of data that may not meet FDA's statutory standards. Nevertheless Congress and others have concluded that such decisions are appropriate. With the appropriate process, the failure to participate will be viewed as a decision, and people can then weigh that action. It is also important to provide people with honest, realistic benchmarks. Objective response rates for oncology products are often in the range of 15-25% when assessed in the "gold standard" of adequate and well-controlled clinical trials. A negative result in a small study may simply reflect an absence of power in the clinical trial, while anecdotal claims of great effectiveness may have no value or merit.

Data are generated from a spectrum of types of studies, from adequate and well-controlled clinical trials and dose ranging studies to pharmacokinetic and dynamic studies and from bioavailability studies to animal mechanism of action studies. Studies done by an NDA sponsor under an IND clearly bear great weight. But studies by the Cooperative Groups also merit substantial weight. Clinical investigators serve in a number of capacities and may produce information of weight in each. Anecdotal evidence has lower value, and it is my understanding that how anecdotal evidence is reported has become a concern for Continuing Medical Education programs in accrediting programs. Mechanism of action data may have unique value. In sum, all have data value.

FDA's regulations establish the content and format for the labeling of prescription drugs, 21 CFR § 201.56. Contained within that format is perhaps the germ of a model for this area. It is a rating system based on data. In the discussion of pregnancy effects and teratogenicty, the agency has an alphabetical rating system that assesses the quantity and quality of data that have been gathered about the teratogenic potential of the drug. The system rates drugs in pregnancy categories; ***A***- if adequate and well-controlled studies have failed to demonstrate a risk, ***B***- if animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women., ***C***- if animal studies have shown a risk

and there are no adequate and well-controlled studies in humans, ***D-*** if there is positive evidence of human fetal risk form drug use based on ADR's, marketing, etc., but the potential for the benefits of the drug's use in pregnant women may make the risks acceptable, and X is the studies show a risk, and the risks clearly outweigh the benefits.

For today patients and the needs of insurers, perhaps the system is too primitive. Other systems exist, e.g., the National High Blood Pressure Education Program, American Society of Clinical Oncology that have alphabetical or numeric coded systems that look at the quality of data that are used in establishing therapeutic guidelines.

V.

An alpha-numeric system may be the best system A system that would qualify the data alphabetically and quantify the data numerically could work well. But it is essential that as much data be made available as possible and in formats that are user friendly and consistent. Of equal importance, the information need not be restricted to the labeling. FDA, for example, posts the monthly therapeutic equivalence ratings in its Orange Book, which is on the agency's website. That rating which has a two lettered alphabetic code that is only considered a recommendation to the state formularies, about therapeutic equivalence. FDA is working ever more closely with the Centers for Medicare and Medicaid Services. States and payors have more and more questions. For these reasons a system that lists the data available on the internet with a rating, I believe may have the optimal value in today's marketplace of information.