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Patient Preferences in Regulatory Benefit-Risk Assessments: A US Perspective

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ABSTRACT

Demands for greater transparency in US regulatory assessments of benefits and risks, together with growing interest in engaging patients in Food and Drug Administration regulatory decision making, have resulted in several recent regulatory developments. Although Food and Drug Administration's Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH) have established patient-engagement initiatives, CDRH has proposed guidelines for considering quantitative data on patients' benefit-risk perspectives, while CDER has focused on a more qualitative approach. We summarize two significant studies that were developed in collaboration and consultation with CDER and CDRH. CDER encouraged a patient advocacy group to propose draft guidance on engaging patient and caregiver stakeholders in regulatory decision making for Duchenne muscular dystrophy. CDRH sponsored a discrete-choice experiment case study to quantify obese respondents' perspectives on "meaningful benefits." CDRH and CDER issued draft guidance in May and June 2015, respectively, on including patient-preference data in regulatory submissions. Both organizations face challenges. CDER is working on integrating qualitative data into existing evidence-based review processes and is exploring options for therapeutic areas not included on a priority list. CDRH has adopted an approach that requires patient-preference data to satisfy standards of valid scientific evidence. Although that strategy could facilitate integrating patient perspectives directly with clinical data on benefits and harms, generating such data requires building capacity.

Keywords: benefit-risk assessment, discrete-choice experiments, patient preferences, regulatory reviews.

Background

The current regulation of pharmaceuticals and devices has evolved from rather different legislative histories. Since Congress passed the Federal Food, Drug, and Cosmetics Act of 1938 (FD&C Act), drug manufacturers are required to provide scientific evidence to demonstrate adequate safety of new products before licensing them for use [1]. The 1962 Kefauver-Harris Drug Amendments in response to public concern over side effects of thalidomide required that drugs must demonstrate efficacy in addition to safety [2]. Based on a review of the evidence, the Food and Drug Administration (FDA) evaluates the safety, effectiveness, and quality of the drugs and makes regulatory decisions. To accommodate the advancement of technological, trade, and public health complexities, the FDA Modernization Act of 1997 amended the FD&C Act and defined FDA regulatory practice for the 21st century [3]. Among other provisions, it reauthorized the Prescription Drug User Fee Act (PDUFA) for an additional 5 years. Initially created by Congress in 1992, PDUFA authorizes FDA to collect user fees from drug companies to provide resources to expedite reviews of new treatments [4]. Subsequent PDUFA amendments require FDA to develop and implement a structured approach to benefit-risk assessment in regulatory decision making for human drug and biological products.

The Medical Device Amendments of 1976 to the FD&C Act created three regulatory classes for medical devices on the basis of risks for human use [5]. Low-risk devices (such as dental floss) require minimal regulatory attention. Higher-risk devices (such as condoms) require greater regulatory scrutiny for safety and effectiveness. Highest-risk devices (such as heart valves) require full regulatory review before they are marketed in the United States. The Safe Medical Devices Amendments of 1990 extended the Medical Device Amendments of 1976 and added reporting and tracking requirements for adverse safety events and effectiveness for the highest-risk devices. Amendments to the Medical Device User Fee and Modernization Act of 2002 later authorized FDA to collect user fees from new medical device sponsors for review activities, and set up specific performance goals for the FDA in terms of medical device reviews [6].

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Patient Engagement in US Regulatory Benefit-Risk Assessments

Regulatory Approaches to Benefit-Risk Assessments Since 2012

US regulatory evaluations of safety and effectiveness of medical products such as drugs or medical devices are based on valid scientific evidence from controlled studies. The FDA considers potential users, intended indications, benefit-risk trade-offs, and the reliability of the drug or device in regulatory reviews. The evidence should support that the health benefits of using the product for its intended indications outweigh the potential risks when accompanied by adequate directions of use. There also should be sufficient evidence demonstrating the absence of unreasonable health risks associated with the use of products for the intended conditions [7].

The Food and Drug Administration Safety and Innovation Act was signed into law in 2012 [8]. Section 905 requires the FDA's Center for Drug Evaluation and Research (CDER) to implement a structured benefit-risk assessment framework in the new drug-approval process. In response, FDA published a draft 5-year plan that describes the framework and its implementation [9]. The key decision factors in the framework include the severity of the condition, current treatment options, benefit, risk, and risk management that may mitigate the potential safety concerns. For each factor, the regulatory decision is informed by evidence and assessment of factual uncertainties. Although the draft acknowledges the importance of quantifying certain components of the benefit-risk assessment, it adopts a structured qualitative approach to identify and communicate the key considerations in FDA's benefit-risk assessment. The agency emphasizes that it is most important to be transparent about what was considered in decision making, and be as quantitative as possible in characterizing the available data.

The 2012 PDUFA V amendments provided financial support for establishing CDER's Patient-Focused Drug Development initiative [10]. This program aims to obtain patients' perspective on disease conditions and available treatments using a more systematic and expansive approach. In 2012, FDA launched the initiative by publishing a proposed list of priority disease areas. Based on public comment, the final list included 20 disease areas that would be the focus of the initiative during the first 3 years [11]. Public meetings are being conducted with participants from FDA review divisions, patient advocacy communities, and other interested stakeholders for the listed conditions. The information obtained from the public meetings helps inform drug-development and regulatory-review processes by giving reviewers a better understanding of challenges patients face in various therapeutic areas, including possible barriers to treatment [12].

Also in 2012, the FDA Center for Devices and Radiological Health (CDRH) issued guidance to clarify the principal benefit-risk factors FDA considers during the reviews for premarket approval applications and de novo classification requests [13]. In addition to a detailed description of benefits and risks, CDRH listed "patient tolerance for risk and perspective on benefit" as an additional factor that CDRH may consider in regulatory reviews. The guidance notes that "risk tolerance will vary among patients, and this will affect individual patient decisions as to whether the risks are acceptable in exchange for a probable benefit. … FDA would consider evidence relating to patients' perspective of what constitutes a meaningful benefit." This was the first indication that quantitative evidence on patient preferences could be considered in FDA regulatory benefit-risk assessments. Subsequently, CDRH established the Patient Preference Initiative to provide the information, guidance, and framework necessary to incorporate patient preferences on the benefit-risk trade-offs of medical devices into the full spectrum of CDRH regulatory processes and to inform medical device innovation by the larger medical device community.

The Medical Device Innovation Consortium, a public-private partnership on regulatory science that includes both FDA and industry members, developed a framework for integrating patient perspectives into medical device benefit-risk assessments [14]. Based on input from the medical device industry, FDA, and patient advocacy groups, the framework defines the concept of patient preferences, discusses various approaches to quantifying preferences, and evaluates how preference information can be collected and used in regulatory decision making. The framework was developed to support the CDRH Draft Guidance and both the Framework Report and Guidance were released simultaneously in May 2015 [15].

Role of Patient Preferences

Weighing benefits and risks of new health technologies requires not only assessing the available scientific evidence but also making societal value judgments about the relative importance of benefits and risks measured in different, noncomparable units. Such judgments traditionally have been delegated to physicians. Increasingly, however, patients are claiming a greater role in such assessments. Availability of valid, quantitative data on patients' tolerance for treatment-related risks could facilitate integration of patient concerns into evidence-based regulatory benefit-risk evaluations.

Patients have unique perspectives about the value of the probable benefits and the impact of potential risks of their medical treatments. Scientists, clinicians, device developers, and regulators play critical roles in understanding the operation of medical devices and the associated benefits and risks. But only patients live with their medical conditions and need to make the choices required for their care. To properly take these views into account, investigators must have reliable and accurate methods, tools, and approaches. Patient preferences would be most relevent where a device is being used directly by the patient, where there are unmet needs, or where quality of life is an important aspect. Submission of patient-preference information is voluntary and may not be suitable for all device areas. Also, such information will not be used as a decision rule, but will be evaluated in conjunction with other regulatory considerations such as legal considerations or quality of evidence.

Patient preference information could be either qualitative or quantitative. FDA regards the more qualitative approach adopted by CDER and the more quantitative approach adopted by CDRH as complementary [16]. Engaging patients through structured meetings elicits direct patient feedback, whereas quantifying patients' concerns with survey data helps integrate such concerns with existing clinical data. Furthermore, the type of information needed could vary at different points in product lifecycles. At discovery and ideation phases of product development, qualitative information on patients' unmet needs, feasibility constraints, and human-factor considerations can help industry prioritize investments in the most useful new health technologies. Subsequently, when conducting structured benefit-risk assessments in regulatory decision making, quantitative patient-preference information obtained from good study designs is needed as part of the valid scientific evidence base when reviewing a marketing application.