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Safety Ethics as Central to the Management of Benefit and Risk

With the emphasis on a global safety system, recent pharmacovigilance inspections in the European Union (EU) have reinforced the reality that there is much more to pharmacovigilance than solely managing case reports. A critical inspection finding is defined by EU inspectors as *a deficiency in pharmacovigilance systems, practices, or processes that adversely affects the rights, safety, or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines*. So there is a need to understand the science behind what constitutes such a system and how it contains processes that protect the rights, safety, and well-being of patients. This understanding can never be spelled out in regulations, nor should it. What is needed is an ethical approach to practically implement such a system and underpin the decisions about benefit and risk.

Ethics should not be solely a theoretical or philosophical set of concepts suitable only for academic debate. Ethics must be practically applied to protect patients' interests adequately. After all, ethics has been defined as practical reasoning—the thought and reason behind our decision-making and choices.¹ Given that benefit/risk decision-making is the fundamental and internationally agreed requirement of safety, understanding ethics is essential to appreciating how and why we make the benefit/risk decisions that we do. More simply defined, then, ethics is “how we know how to do the right thing.”

There is considerable published experience in other safety-conscious organizations and industries, outside the pharmaceutical sector, about how the ethics of safety is central to effective operations and customer service.² From this experience, we can better understand how value judgments are imbedded in the information available. This is particularly important in safety, where much scientific information contains uncertainty and may easily be thwarted by different value judgments.

What has benefit/risk management to do with good clinical practice (GCP)? The concept of balancing benefit and risk, which is supported by the processes that constitute pharmacovigilance, is central to the application of GCP globally, as indicated by this statement from the International Conference on Harmonization (ICH) GCP Principle 2.2: “A trial should be initiated and continued only if the anticipated benefits justify the risks.” Indeed, the applicability of balancing benefit and risk to all forms of research goes right back to the Nuremberg Code, which states, “Risk to subjects should be minimized and justified relative to anticipated results.”

The Declaration of Helsinki, which arose out of the Nuremberg Code, made balancing benefits against risk one of its central themes. The authors of the declaration introduced the concept of justified risk, referring to risks that were

justified by the “potential diagnostic or therapeutic value to the patient.” For those who drafted the declaration, the message was simple: Balancing risk and potential medical benefits was a fundamental requirement for all research.

The Belmont Report of 1978 reinforced the research requirement of favorable benefit/risk balance.³ Internationally, as described in a recent U.S. Institute of Medicine report, when we talk of a safe medicine we mean one with an acceptable balance of benefit and risks.⁴ In that respect, there is harmony among regulatory authorities concerning what they expect from the pharmaceutical sector when they refer to “safety.”

Society's Changing Approach to Benefit and Risk

What constitutes an acceptable balance of benefit and risk changes with the social climate. In the 1960s and 1970s, protecting individuals from risks prevailed. In the 1980s, the social context changed, driven by AIDS and cancer patients who argued that overprotection and undue precaution caused unacceptable risk. Since about 2000, the pendulum has swung back to focus on risks for several reasons. In the U.S., investigations into the death of the trial subject Jesse Gelsinger and claims from participants in other trials that they were not adequately informed of the risks pointed to deficiencies in the benefit/risk decision-making process and regulatory oversight. Ultimately, this clamor led to the establishment of the Office of Human Research Protections and a more scrupulous approach to risk in research.

Meanwhile in the EU, although unrelated directly to concern about pharmaceutical safety, an important political declaration in December 2000 at the

EU's summit in Nice, the Charter of Fundamental Rights of the EU 2000/C 364/01 underpinned the thinking and rationale behind all further regulation about safety and pharmaceuticals. This charter sets out a whole range of civil, political, and social rights enjoyed by all EU citizens. It is divided into six chapters: Dignity, Freedom, Solidarity, Equality, Citizenship, and Justice. The charter covers everything from social rights to bioethics and the protection of personal data. It is not legally binding, but is meant to be taken into account by individual national law courts and the European Court of Justice. The sections that are directly relevant to safety are described in Table 1.

As a result, those who work with pharmaceuticals should be aware of the way the EU Charter is an addition to the European Convention on Human Rights, which is overseen by the Council of Europe (<http://www.coe.int>), which acts as the guardian of democratic security. This convention, signed in 1950 by the countries that make up the Council of Europe, is enforced by the European Court of Human Rights. Established in 1949 and representing 46 countries (more than just the EU), including 21 countries from Central and Eastern Europe, the council has the following mission:

- to defend human rights, parliamentary democracy, and the rule of law;
- to develop continent-wide agreements to standardize member countries' social and legal practices; and
- to promote awareness of a European identity based on shared values and cutting across different cultures.

Ethical standards fall within the remit of the charter, and what constitutes risk in research is described in detail in the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research Strasbourg. Even though the Declaration of Helsinki is already reflected in the charter, the Additional Protocol enshrines the

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declaration at the center of all research.⁵

⁶ The Additional Protocol expands on the ethics of what risk means to patients and how to manage this risk; so the research community needs to be fully apprised of this critical document to understand how to conduct ethical research and what risk means within the EU. Failure of those outside the EU to appreciate this may lead to surprising opinions about the safety of a procedure, or even a whole study, which elsewhere in the world might not have engendered the same reaction.

The concept of human dignity is the essential value to be upheld and is the basis of most of the values emphasized in the Additional Protocol, significantly shaping the European view of risk. Traditionally, society has linked risk to “harm” in the sense of physical damage, which in the case of medicines, means adverse reactions. However, the Additional Protocol has now expanded the definition to less tangible forms of harm, such as loss of trust or damage arising from deception. Thus “failure to comply with a trial or activity” is risk, which might mean patients will feel unsafe. The concept of “negligible risks of harm” is now obsolete, as questions about social contacts—as well as relationships, family, and employment in the right context—could easily be emotive risks. Ethics committees now have a fundamental role in judging what constitutes

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acceptable risk in the context of a patient's human rights.

Furthermore, lack of appropriately informed consent for involvement in research or experimental treatment can raise issues under human rights legislation. In Denmark, the European Commission of Human Rights concluded that medical treatment of an experimental character and without the consent of the person involved may, under certain circumstances, be regarded as a breach of human rights under the prohibition of torture or inhuman or degrading treatment.⁷ Hence, clinical research associates (CRAs) need to practice close vigilance over the consent procedure, as this is the first step in collecting patient-generated safety information.

Understanding the broader meaning of risk is directly relevant to interventional clinical trials because, as stated in section 3.3.8 of ICH GCP, "Investigators should promptly report changes increasing the risk to subjects and/or significantly affecting trial conduct, such as new information that may affect adversely the safety of the subjects or the conduct of the trial." Training programs in GCP should contain a more comprehensive explanation of what risk is and what should be communicated to authorities and patients. In particular, a more holistic patient-focused approach is now warranted for annual safety reporting showing that the sponsor is sensitive to the risks that matter to patients.

As an example of an emotive risk, which occurred during a real trial, CRAs started to receive calls from worried trial participants who read in the press that the trial sponsor was in financial difficulty. They were worried that the trial would be stopped prematurely. To manage risk in the future, one could argue that a sponsor faced with a similar situation should alert patients about it early and assure them that enough funds exist to enable successful trial completion.

The discussion about risk in this context has caused confusion about the meaning of the term "intervention," especially with reference to the way the European Commission has defined an interventional study.⁸ For the purposes

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of the Additional Protocol, intervention can be either a traditional physical intervention or any other intervention insofar as it involves a risk to the psychological health of the person concerned. Thus, paragraph 17 states that intervention must be understood in the context that it includes all physical and nonphysical actions (for scientific research purposes) relating to the health or well-being of persons. This would be incompatible with FDA advice of June 2004, which suggested that clinical research projects conducted abroad need no longer comply with the Declaration of Helsinki.⁹ As this contradicts the European position (including the EU), this may explain why organizations outside the EU find it difficult to negotiate the European ethical maze of what is and is not an acceptable risk in a clinical trial.

As there is no generally applicable categorization of "risk," discussion is needed on a case-by-case basis. This has enhanced the importance of understanding ethics in, for example, successfully understanding how to communicate benefit/risk during the consent procedure and producing and keeping up-to-date product information for doctors and patients. In essence, it is all about better understanding what really worries doctors and patients and what they need to know relevant to that particular territory.

It is not just the so-called developed world grappling with defining adequate benefit and risk. The participants in trials in developing countries are often prepared to accept the risks of being in a trial, but only if there is adequate after-care or provision of free product.¹⁰ In the Declaration of Helsinki 2000, paragraph 8 refers to populations who need special protection, such as the economically disadvantaged. This infers that such patients may be willing to consent to

greater risks if there are no or limited alternatives to treatment and medical care—in effect, acting as "undue coercion" and as a possible unacceptable risk.

This creates challenges concerning how different cultures define risk and free will, and how one should tackle literacy and language barriers. In recognition of these concerns, as part of the EU Commission's Science and Society program, NEBRA is a collaboration of 15 West African countries that want to improve their ethics review procedures to fulfill international requirements. This interesting project has shown how ethical values differ between northern and southern countries in that region, which in turn is related to differing perspectives on benefit/risk.¹¹ How the ethics of benefit and risk is managed in developing countries is clearly an emerging issue of importance as the Asian pharmaceutical sector expands. Even an experienced organization such as the Centers for Disease Control ran into difficulties with differing interpretations of what was acceptable risk in the tenofovir trials.¹²

Confusion Between Compliance and Ethics within Pharmacovigilance

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other words, externally imposed obligations, whereas ethics focuses on values. However, in reality, ethics helps compliance in those grey areas not covered by law or regulations, which is particularly relevant to safety and risk management. Compliance is more than SOPs and training. In order to comply with regulations, compliance needs ethics, as one cannot rely on improving compliance just by reminding people to “be more careful.” Thus, being ethical reduces the risk of noncompliance and, in effect, is an intrinsic part of being compliant.

This is well-illustrated by the EU pharmacovigilance guidelines (Volume 9), which include an expectation that marketing authorization holders manage benefit/risk of their products. As discussed earlier, this requires ethical insight into how the different EU populations view acceptable risk and benefit in their own member state. As described in Article 16(2) of Regulation 726/2004, marketing authorization holders are expected to notify regulatory authorities of safety concerns, that is, any new safety information that might influence the evaluation of the benefits and risks of a product. The process of what new safety information to expedite and what not requires ethical interpretation. Too many expedited signals might conceivably overburden the system and potentially obscure true hazards.

If the pharmaceutical industry wants to look for evidence as to how to move toward a culture where safety ethics values predominate, then the vast amount of evidence that has accrued from other safety-conscious industries should be analyzed.² From this evidence, certain conclusions are obvious. Improving compliance is about changing the company culture from one of blame to one where systems are examined from beginning to end to reduce the opportunities for mistakes and learn from errors.

Traditionally, ethics has been regarded as an individual issue whereby employees followed the company’s code of conduct. Although the behaviors of individuals determine an organization’s ethical culture over time, altering processes and practices can change ethical

values, beliefs, and attitudes. When decisions and activities do not occur as planned, as part of their root cause analysis of poor compliance or ethical decisions, managers should pay attention to human factors such as limited memory capacity and the negative effects of stress, fatigue, distraction, interruptions, and multitasking. As other industries have shown, human factors are the major cause of poor compliance with safety. This is an urgent topic for the education and training of pharmaceutical employees.

Many courses in ethics rightly consider confidentiality, trust, consent, and the competence and autonomy of the patient. However, when it comes to making decisions about benefit and risk, previous curricula have omitted the reality that these decisions are made in a tough commercial environment. One only has to reflect on the pressures on the National Institute for Clinical Excellence and its German equivalent, the Institute for Quality and Economic Efficiency in Health Care, to illustrate the difficulty society has with the economic realities of new medicines.

Ethical Business Practice is the Basis of Good Business Practice

Finally, it is important to note that management schools place great emphasis on ethical culture as part of good business practice. A senior regulator, William H. Donaldson, who was the chairman of the U.S. Securities and Exchange Commission, acknowledged this importance: “The most important thing a Board of Directors should do is determine the element that must be embedded in the company’s DNA. . . . It should be the foundation on which the Board builds a corporate culture based on a philosophy of high ethical standards.”¹³

But what is this DNA? It is derived from a model for defining the type of organization a person is working in, and can be helpful as a diagnostic tool for improvement and to help initiate dialogue. This is a useful model for understanding how organizational behavioral, emotional, and cultural factors interplay to influence an individual’s ethical be-

havior and affect his/her performance when having to make benefit/risk decisions in a commercial environment.

The two strands of this DNA consist of financial integrity and safety (benefit/ risk), with the following four building blocks of organizational DNA (“nucleotides”):

- **Decision rights:** The underlying mechanics of how and by whom decisions are truly made. In reality, it goes beyond the lines and boxes of the traditional company organizational chart.
- **Information on which decisions are made:** What metrics are used to measure performance? How are these new activities coordinated, and how is this knowledge transferred to the larger organization? And, because budgets are limited, what impact does that have on safety; and how transparent are those decisions?
- **Motivators:** What objectives, incentives, and career alternatives do people have, and do they work in an organization that values the safety professional? How are people influenced by the company’s history and previous approach to balancing benefit/risk?
- **Structure of the organization including the “lines and boxes” of the organogram:** Is there a mismatch between the organizational structure and the strategic intent of an organization?

Such a model can be useful for teaching the ethics of safety decision-making by applying all four components.

Conclusions and Recommendations

The pharmaceutical sector would be well advised to examine the mass of evidence currently available from other safety-conscious industries about safety ethics decision-making when preparing to tackle its own issues in this arena. Other industries mingle, share safety stories, and identify common methodologies for

managing risk and rebuilding trust. In contrast, the pharmaceutical industry is rather parochial.

In addition, safety ethics training is required for all those involved in making safety decisions. All such company managers and employees need to be exposed to sets of simulated experiences in which they confront, question, and reflect on the core values that run through the whole company in all its decisions, operations, and stakeholders.

Understanding and actively managing ethical conflicts that arise during benefit/risk decision-making about pharmaceuticals is critical to progress in this area and restoring trust in the international system of safety.

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Brian Edwards, MD, is one of the deputy-qualified persons for pharmacovigilance within Johnson & Johnson. Previously, he worked in pharmacovigilance at Parexel and the UK Medicines Control Agency. He is treasurer for the International Society of Pharmacovigilance and active in the clinical safety and pharmacovigilance SIAC for DIA. He chairs the panel, appointed by the UK Faculty in Pharmaceutical Medicine, overseeing the Drug Safety Surveillance module as part of higher medical training. He can be reached at BEDwards@brmgb.JNJ.com.