Editorial Commentary

Fifty years after thalidomide; what role for drug regulators?

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Fifty years ago, in December 1961, a letter from an Australian obstetrician alerted the world to thalidomide-induced teratogenicity. That tragedy became a key driver of the evolution of evidence standards for drug development and licensing. It also reinforced the notion that a knowledgeable and trusted third party – the drug regulator – is needed to protect patients' interests and to decide for them which drugs would be available to them; this is allegedly because patients are not able to make informed decisions about such complex matters as drug treatment and manufacturers could not be trusted to present information on their products in an unbiased way.

Time has not stood still since thalidomide, and societal perceptions of surrogate vs. autonomous decision making are changing. Some are generally distrustful of government interference in personal matters; some would argue that drug regulators have lost public trust in the wake of high-profile drug safety issues.

Patients can now obtain information (and misinformation) on drugs without intermediary. A push for transparency results in more public availability of clinical trial data [1]. Patient and consumer organizations are presenting study results in patient-friendly formats, reducing information asymmetry between patients and drug manufacturers.

Patients have become more vociferous in their demands to gain access to new drugs and to make individual treatment decisions. Historically, the most significant event along this evolution was the intervention by HIV activists who told regulators, 'nothing for us without us'. More recently, patients with multiple sclerosis have demanded access to a drug that regulators deemed too dangerous, and breast cancer patients pleaded to keep a drug licensed for an indication for which regulators deemed it ineffective.

Patient representatives emphasize that regulatory approval and refusal are not symmetric actions; when a drug is approved, an individual patient has a choice to take

it or not, whereas when regulators refuse to license, that choice is gone.

So, has the time come to treat patients as mature consumers and allow them to make their own decisions about drugs? Is there a future for drug regulation in its current form?

Regulatory decision making comprises two different assessments. First, in a logical order, comes an assessment of the quality and adequacy of data; second is an assessment of whether the expected benefits outweigh the expected harms. Let us initially consider the second assessment and imagine a world of perfect information where all beneficial and harmful effects of a drug and their probabilities in defined patient subgroups are known. In the absence of uncertainty, the decision to take or not to take the drug is reduced to balancing the expected utility of the benefits against the expected disutility of the harms. 'Expected utility' describes the probability of an outcome (good or bad) multiplied by some form of value weighting, often referred to as (dis-)utility weight. In this hypothetical scenario, the willingness to trade benefits for harms is driven by the values assigned to different symptoms or health states. This observation begs the obvious question: whose values should count?

Most drug regulators do not have the specific disease experience and do not take the drugs they authorize. Patients, on the contrary, know which outcomes and symptoms matter most to them, and they are the ones who incur the risks from drug treatment. It seems self-evident that patients' value judgements ought to be paramount. In a democratic society, patients should not be told by surrogate decision makers whether their relative disutility of a heart attack should be higher or lower than that of a stroke, provided that these events are properly described to them.

There are few treatment scenarios where patient preferences may not be the only decision criterion and public health considerations (e.g. development of microbial

resistance) might legitimately influence a decision on the availability of a medicine. Occasionally, patients' value judgements may be called into question. For example, some teenagers would probably be willing to accept a small risk of a lethal adverse effect from a drug that reliably cures their acne. Yet, society might be uncomfortable seeing teenagers die from acne drugs.

Notwithstanding such rare exceptions, in an idealized world without uncertainty where treatment consequences can be clearly explained to patients, the role of the drug regulator should be quite limited.

Alas, we do not live in this ideal world. All regulatory decisions are taken in conditions of uncertainty, and this is where the first of the two regulatory assessments comes in, judging the quality of data.

Modern evidentiary standards of drug approval have greatly expanded our ability to predict the effects of drugs, but the interpretation of study data, or the act of distilling raw data into useful information, has become a science in its own right.

The detection of hidden bias in a randomized trial, extrapolation of study results across patient populations or the identification of areas of missing information are not trivial tasks. It is instructive (though not necessarily reassuring) to watch seasoned clinicians, statisticians, epidemiologists and other regulatory experts vehemently disagree with each other over these issues.

Manufacturers are legally compelled to 'not lie' about their products, but patients may still be deceived. A statement by a drug manufacturer that 'there was no statistical difference between treatment groups' may be technically correct and may appear convincing to patients, but the statement is meaningless in the absence of interpretation of assay sensitivity of the clinical trial on which it was based.

Non-expert patients are unlikely to be in a position to make these interpretations. Also, too great is the temptation for the human mind to infer causality when observing temporal relationships: 'I took this drug for many months and I am still well and alive. This is *proof* that the drug works for me'. Testimonials like this and requests for ineffective treatments can be maddening for scientists and regulators, as are unrealistic expectations of guarantees of safety.

We argue that in a world of uncertainty and complex data sets, information asymmetry has not disappeared and there continues to be an important role for drug regulators to protect patients from themselves and from those who might exploit them. This may sound all too obvious to the scientific community, but it is not an excuse simply to perpetuate the current regulatory paradigm of proxy decision making.

How, then, can we combine respect for patients' value judgements with scientific rigor? We return to the notion that benefit-harm decisions are inherently about expected utility, the product of probabilities (derived from 'objective' data) and utilities (value judgements that are necessarily subjective).

The drug regulatory system is strong on the data side. Regulatory assessment reports are explicit about risk estimates, hazard ratios or other measures of the probabilities and uncertainties of the good and bad consequences of drug treatment.

Yet the same reports are usually silent on value judgements. This is not to imply that values and preferences do not come into regulatory decisions – they have to – but they are inserted implicitly. There are few cases where regulators have explicitly discussed the notion of values of health outcomes [2], and we are not aware of regulatory decisions that have quantified patients' values or willingness to trade benefits for harms. In the absence of patients' values, regulators will need to bring their own value systems to bear on benefit-harm decisions [3].

Methods for eliciting patients' utilities are available. There is a substantial body of methodology experience, and patient preferences and utility weights have been gathered for a surprisingly large number of symptoms and health states.

There is also a range of decision tools that enable the structured input of probabilities of outcomes, uncertainty and explicit values; they include decision trees, multicriteria decision analysis and others. We have tested a number of methodologies that might be used to incorporate patient values into regulatory decisions [4].

Some of these tools and applications may be contested on the basis of methodological weaknesses, and most of them have not been used by regulators. However, this is not a legitimate excuse for wholesale dismissal but should prompt the scientific and regulatory community to assess their merits or shortcomings.

Where should 'values' come from? Patients enrolled in regulatory drug trials are (ideally) the target group for treatment once a drug is licensed, yet we do not usually explore their values and preferences in a systematic way. In terms of listening to the patients' voice, trial patients are an underutilized resource. Most trial patients would probably be willing to share their health values and preferences by way of structured interview, questionnaire or other interactive methods, at limited additional cost to sponsors. These findings should be made public, like any other trial results, and explicitly incorporated into regulatory decisions.

What could be done? Ambitious projects have been launched to improve drug development and drug regulation. Research partnerships like the Innovative Medicines Initiative and the Critical Path may be ideal platforms to test existing methods and develop new tools for systematic assessment of patient preferences and for supporting the regulatory decision process.

The pay-off from such projects would be significant, in that combining patients' value judgements with the technical expertise of regulatory scientists is expected to enhance the legitimacy of and public trust in the licensing process. Fifty years after thalidomide, there is still an important role for drug regulators, but the time has come to

bring patients fully into the decision process, as equal partners.

Competing Interests

There are no competing interests to declare. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies and organizations for which the authors work.

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