**Yellow lights for emerging technologies**

All-or-none regulatory systems are not adequate for revolutionary innovations

*By R. Alta Charo*

There is an infuriating, often confusing four-way stop intersection near my home. The city refuses to install traffic lights, because devices such as roundabouts, four-way stop signs, and flashing yellow lights, which require drivers to slow and scan before entering, can result in fewer accidents, as well as a faster and more even flow of traffic. There is a lesson to be learned here for regulation of new technologies. Clear, decisive rules are seductive. New drugs cannot be sold untold until proven safe. Food supplements are sold until proven unsafe. Although such clean demarcations can be reassuring, they do not work well for technologies whose applications cannot be presumed safe or unsafe.

Technology innovates faster than the regulatory system can adapt, whether with innovative modes of governance or interpretations of standard regulatory models (1). Emerging technologies, such as nanotechnology, synthetic biology, and gene editing are characterized by rapidly evolving scientific understanding of fundamental mechanisms; novel application possibilities; parallel development of measurement and evaluation tools; and public reactions that include excitement and concern. The uncertainties of emerging technologies can make it difficult or even impossible for regulators to apply traditional risk-benefit analyses, because they may have neither a definitive idea of what to look for nor a means to identify it. Yet waiting to satisfy these methodological and data needs could effectively block technology deployment, deny possible benefits, and possibly forestall developing data to resolve the uncertainties.

The White House issued a set of principles (2) for regulating emerging technologies: scientific integrity, public participation, benefits and costs, flexibility, risk assessment and risk management, coordination, and international cooperation. Perhaps the most interesting and important is “flexibility.” The challenge of combining flexibility and public trust is that, in the absence of confidence in the regulatory system’s independence, integrity, and ability to revisit earlier decisions, trust can morph into a demand for rigid protections against the unknown.

A prime example of this tension is the history of genetically engineered (“GE”) foods. Food regulation comes in two basic flavors. There is a lengthy, onerous rule-making process for food additives that can take an average of 6 years in the United States (3), or even more in Europe (4), versus a streamlined, largely self-enforced process for foods that are “generally recognized as safe” (“GRAS”) (5) that allows producers to market their products immediately and indefinitely with little U.S. Food and Drug Administration (FDA) involvement, unless the agency subsequently proves that the food is not safe for its intended use (6).

For GE foods, companies generally follow a voluntary consultation process with the FDA to confirm GRAS status, because the agency has found nothing in the biotechnology process inherently unsafe. But opposition to these foods and calls for more regulation are far from abating. An innovative process that legally required greater involvement by the FDA or the Department of Agriculture (USDA) before and after these foods were marketed might have helped to quell concerns without slowing innovation. Indeed, USDA recently initiated a stakeholder consultation process to consider whether and how to change the current system (7).

When another technology comes around, e.g., the use of nanotechnology to change the size (and potentially, some properties) of common ingredients, it may not be possible to categorically label it as GRAS or non-GRAS. The choice, again, is between stifling innovation with rule-making or losing public confidence owing to voluntary procedures based largely on industry-driven research.

There are tools that might add flexibility, many already used in some area of regulation. Restricted approvals put limits on how a product can be purchased, such as requiring certain medical tests be performed before a drug may be prescribed. Conditional approvals impose penalties or approval withdrawal if manufacturers do not submit the follow-up information. Sunset clauses withdraw approval automatically when conditions are unmet, without the need for the agency to satisfy a burden of proof before a court or other arbiter. Marketing restrictions place limits on how a product can be advertised. One observer describes these various approaches as “experimental” noting that “[e]xperimenting with laws can be particularly useful to test new regulations on a small-scale basis, gather more facts on the response of the market to an innovative product, and improve regulation as more information becomes available” (8).

But innovative tools must be deployed properly. In 1972, the FDA developed an intermediate option when problems are detected in marketed foods. The agency would use a category of “interim” food additive for the time it would take to resolve the issues (9). The interim food additive status gave the FDA the power to impose limits on the food’s marketing while the requested studies were completed. But this option has been used infrequently, and in some cases, the interim status has become an indefinite label. Overall, it has not resulted in more aggressive FDA oversight of foods marketed as GRAS (IO).

The European Medicines Agency’s efforts to implement a system of conditional drug approval that might get drugs out more quickly but with greater regulatory control does not have measured outcomes. The European Commission has created two pathways. The first works for drugs for which it is not possible to provide the European Medicines Agency with additional data, a category that might be interpreted to include drugs based on novel technologies. The second, called “conditional approvals” (CAs), allows drugs to enter the market with less than the usual level of safety and efficacy data, if they have a good risk-benefit ratio demonstrated in initial trials, and it is expected that more data will be obtainable once marketed.

In some ways, this resembles the proposals made in the United States to increase use...
of biomarkers and surrogated endpoints, with postmarket demonstration of clinical endpoints to follow. But the European CA does this without losing tight control over the medication, because conditionally approved drugs lose their approval status and are removed automatically from the market if sponsors fail to meet their postmarket commitments for further trials (17). Early indications are that the system has not increased the frequency of problems with drugs approved under this process (12), although, in a similar Canadian system, the number of postmarket warnings and drug withdrawals is higher than that for drugs receiving standard (and lengthier) premarket review (13).

In the United States, withdrawal of a marketed drug takes positive action. Under conditional approval in the European Union, the mere failure either to submit postmarket data to support the initial release or to apply for a limited-time renewal of the conditional approval means that the drug can no longer be marketed. But this approach, which reduces time-to-market for innovative drugs while maintaining strong tools for public health protection, has not been extended to emerging technologies generally.

Analogously, in the conditional registration system for agricultural pesticides, new active ingredients are moved to market with the condition that the U.S. Environmental Protection Agency (EPA) receives additional data. It is limited to circumstances (similar to the interim food additive rule) in which the agency can demonstrate that the product does not pose a threat. It also is limited to situations in which a sponsor did not have enough time to meet agency requests for specific data and in which there is a significant public need for the new product. It is not, however, aimed at products based on emerging technologies for which there may be initial safety data but for which additional data on safety and benefits will be developing over the next few years (16).

Another example of the conditional approval approach comes from Japan, where recent amendments to their pharmaceutical law allow sponsors to seek short-term market approval for stem-cell therapy products, provided that early studies show promise. While on the market, these conditionally approved therapies are eligible for reimbursement (15). The effect is to put a lot of pressure on postmarket surveillance and responsive regulation (16). For particularly controversial technologies, such as embryonic stem cell therapy, early introduction poses a risk that any high-profile failure might increase political opposition or public skepticism, as happened in the field of gene therapy (17).

Another obstacle to developing and deploying a wider variety of restricted, conditional, and sunsetting regulatory actions is the need for new legislative authority under which new regulations might be issued. Although the 21st Century Cures Act (18) is being discussed in Congress, there is no evidence of a broader legislative agenda. Also, our tort system cannot act as a regulator, given that it depends on attention to industry-set or customary practice standards, which for emerging technologies will not yet have been formed.

The problem may sort itself out without explicit attention from lawmakers. When emerging technologies create uncertainties, a regulatory gap can emerge along with the technology. Into this void can flow professional self-regulation, as happened with recombiant DNA and human embryonic stem cell research. The scientists proceeded to devise and implement guidelines with such success that they eventually became the basis of government regulation and funding policy. In neither case was the emphasis on declaring technologies or applications inherently acceptable or not. Rather, guidelines took a provisionally precautionary approach toward the risk of environmental release or physical harm to humans, without putting a halt to the work entirely.

The recent call for a temporary moratorium on clinical attempts to use CRISPR-Cas9 for human nuclear DNA germline editing may provide the same pause for reflection (19). Within months, the U.S. National Academies announced an initiative that would include both an international summit and a consensus study committee. But the central challenges remain: For a technology whose effects might reverberate for generations, is it possible to have enough information to satisfy risk-benefit analyses? Who has the moral authority to make the decision to proceed? To the extent that it is “the public,” experience tells us that the venues are limited (e.g., testimony to presidential bioethics commissions or expert advisory committees) or risk being captured by ideological agendas. Other countries have been more comfortable including public opinion and morality-based arguments in their technical decisions, e.g., in the United Kingdom’s regulation of regenerative medicine through a comprehensive licensing body. But such centralized control runs into political and even constitutional obstacles in the United States.

A more iterative process would incorporate a variety of tools, designed to enhance partnership between industry and regulators through an expanded range of consultation processes and postmarket reviews; enhance transparency of developing data, including data about failed trials and experiments; incorporate limitations on advertising and applications while research continues; put the burden of producing information to maintain approval on the sponsors; ease the burden on regulators who seek to add protections or withdraw problematic products; and continually reevaluate the real benefits and harms. It would also provide increased access to existing venues for public discussion and legislative action, as well as new opportunities at the state and local level for community education and discussion. This might include greater use of temporary moratoria that allow the public to catch up with new information and reflect on the implications of new technologies.

Iterative regulation, constant monitoring and reevaluation, wider consultation, and a broader array of conditions and restrictions may at times be confusing, but they also might forestall a regulatory “no” or prevent public outcry over a regulatory “yes,” either of which can, in the end, slow innovation. One might say that what we need are more roundabouts, four-way stops, and yellow lights to supplement our red-light, green-light regulatory system.

REFERENCES


“Technology innovates faster than the regulatory system can adapt...”

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Editor's Summary

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