nature biotechnology

20 years of bio-lox

Here's hoping that a proposed shakeup of US regulations will mean that new biotech products avoid AquaAdvantage salmon's two-decade upstream struggle to regulatory approval.

November marked the first US approval of a genetically engineered food animal. AquaBounty Technology's salmon, genetically engineered to constitutively express growth hormone, has had a long journey; 20 years, two months and five days to be exact, from investigational new animal drug submission to approval. It has negotiated the eddies of stakeholder deliberations and public consultations, swum in ever-decreasing circles while agencies wrangled over jurisdiction and elaborated new rules, and leapt through advisory committee hoops until finally pronounced "as safe as food from conventional Atlantic salmon," only to be caught in three years of citizens' petitions and political stonewalling before its final release last month. All this suggests that the US regulatory system for biotech—otherwise known as the Coordinated Framework for the Regulation of Biotechnology—may not be fit-for-purpose when it comes to novel biotech products that fail to fit existing categories.

This may be one reason why the US Science and Technology Policy Office (OSTP) has started to update the Coordinated Framework. OSTP is seeking feedback on (among other things) which agency has statutory authority over which new types of products, whether overlapping responsibilities among agencies need streamlining, and how well communication between the agencies and consumers, industry and other stakeholders has worked. It has already held a public meeting on the issue (p. 1221)

The Coordinated Framework certainly needs an overhaul. It was last upgraded in 1992, at a time when a fish with a single-gene transgene was 'state of the art'. Then, using a single Chinook salmon growth hormone gene controlled by an antifreeze protein promoter and terminator from ocean eelpout to develop a fast-growing Atlantic salmon was a technical advance.

But a lot has happened since. Researchers have begun to use synthetic DNA in addition to cloned recombinant DNA. They reboot chassis organisms with refactored genetic material. They engineer multiple genes and stack traits to create plants and animals. Animal breeders use somatic cell nuclear transfer. Investigators are now exploring the possibility of xenonucleic acids (beyond A,T, C and G) as genetic material, and changing the triplet code to incorporate unnatural amino acids. The organisms that could be developed might be as distinct from today's livestock and seedstock as those organisms are from their 'natural' pre-agricultural progenitors.

Changing genes is becoming more facile and more rapid. There are now over a dozen gene transfer methods, beyond the standard workhorses of *Agrobacterium tumefaciens* and biolistics. RNA interference and oligonucleotide-based mutagenesis are in common use. Gene editing techniques, such as zinc finger endonucleases and transcription activator–like effector nucleases have been joined by CRISPR-Cas9, a tool of unprecedented power, speed and ease of use.

Can all this be packed into the present regulatory system? Even at its start 30 years ago, regulatory agencies were already stretching definitions within the old Coordinated Framework; this is why the Environmental Protection Agency regulates genetically engineered plants as "pesticides" or "plant-incorporated protectants"; the US Department of Agriculture (USDA) regulates transgenic plants as "regulated items" under "plant pests"; and the US Food and Drug Administration (FDA) regulates transgenic animals either as food or animal feed or as "animal drugs."

What sometimes seems important to regulators is not that biotech products are safe and efficacious but that they can be regulated. Thus, USDA invented the term "regulated article" to capture all recombinant DNA plants, regardless of potential risk. The FDA, in contrast, usually assesses the safety and efficacy of foods and drugs on a case-by-case basis and may choose *not* to regulate if it deems a product poses no public health risk. It did just that in 2006 in the case of the GloFish—a zebrafish engineered to glow red destined for pet stores.

A fundamental revision of the Coordinated Framework is needed so that regulatory agencies do not simply continue to ignore its founding principles. At the moment, they continue to single out bioengineered products for blanket scrutiny when the framework emphasizes that oversight should be based on the risk posed by a particular product and not on that product's technical origins. Clinging to a process-based implementation of regulation, as many activists and special interest groups want, means trouble. Technology, and biotechnology in particular, will always outpace regulators and their proliferation of rules.

An organism engineered by means of CRISPR-Cas9 gene editing, for instance, might simply evade the regulatory process. It would likely be indistinguishable from another organism expressing the same trait produced by conventional breeding and thus, presumably, not be a USDA-regulated article or subject to FDA's recombinant DNA techniques. As newer products shed the detectable transgenes or marker tags, process-based regulation either becomes untenable or requires a perverse extension of rules for regulatory capture—"anything produced by an organization that spends money on R&D" might cover it. Technology changes; product traits remain product traits.

Is the Coordinated Framework ready for the new types of product coming out of biotech? Probably not. But make no mistake, these products are coming, and they will come faster than ever before.

For OSTP then, the focus should be on reinforcing the Coordinated Framework's credentials as a science-based, well-defined and predictable regulatory system—and making it as immune as possible from political intervention. As OSTP stated in 1992, additional regulation is warranted only when "the value of reduction in risk obtained by additional oversight is greater than the cost thereby imposed." The emphasis should be on harmonizing different agencies, streamlining regulation and, yes, deregulating products that are of low risk despite being products of bioengineering. It is incredible that AquaAdvantage is still around after its 20-year wait for approval. Future biotech products might not be that lucky.