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Regulatory barriers to improving global food security

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ABSTRACT

Crop agriculture and food production constantly face climactic challenges to the supply of safe, nutritious food. These challenges highlight the importance of innovation resulting in improved crop technologies, capable of providing consistently increasing yields in the face of abiotic and biotic stresses. This article addresses the challenge that regulatory barriers are, and can, have on the adoption of innovative crop and food technologies that improve food security. Evidence of increased crop yield and the potential for increased yields, are presented from innovative plant breeding technologies, especially gene editing. Recent advances from the use of gene editing in the pharmaceutical field may offer opportunities to reduce regulatory burdens.

1. Introduction

Federal regulatory frameworks were established over a 6–8 year period in the 1990s, to undertake science-based risk assessments of what became to be known as genetically modified organisms (GMOs) (Khoury and Smyth, 2007; Gleim and Smyth, 2018), with the initial genetically modified (GM) crops being commercialized between 1994 and 1997. Since GM crop risk assessments began, over 4300 science-based risk assessments have been conducted by regulatory agencies in 70 countries (ISAAA, 2019). To date, no GM crop or food has been found to have a level of risk that is significantly different than that of conventional crop or food products. In spite of quantified scientific risk assessments, political interference has taken place, and is taking place, delaying or preventing commercialization of GM crops and food products. The cost of delayed adoption can be significant, as delays of six years are capable of reducing a firms' return on investment to the point that the investment will not be made, given the high level of regulatory uncertainty (Smyth et al., 2014). Efficient regulatory systems that make repeated, timely decisions are essential for investment and innovation in agriculture. Without efficient regulation, gene-edited crop varieties that can improve food security, will be delayed or abandoned, rather than be commercialized.

The science of genomic research technologies has advanced rapidly, moving from genetic modification, where a gene, or genes, are inserted into one plant variety from another plant variety (i.e. herbicide tolerant varieties) or from one species into another (i.e. insect resistant varieties), to the recent explosion of gene editing research. Gene editing offers significant advantages to plant breeders, given the controlled precision offered through the editing tools, especially compared to the random mutation effects from chemical or radiation mutation. Regulatory barriers to gene-edited varieties exist as regulatory risk assessments struggle to keep pace with the rapid rate of innovation. This is particularly the case where regulatory systems are process-based, rather than product-based. Investment in gene editing crop development research in the European Union (EU) has declined following the 2018 decision by the Court of Justice of the EU (CJEU) that gene-edited crop varieties must be regulated as equivalent to GMO varieties (Smyth, 2019).

This article reviews the application of gene editing technologies to crop variety development, highlighting the challenges that exist between regulatory systems that are science-based and product focused, compared to precautionary-based regulatory systems that are process focused. Following a review of recent gene editing innovative advancements, the policy dilemma is thoroughly investigated. The article concludes with a concise summary.

2. Effects of regulatory burdens

Targeted, controlled plant breeding technologies, such as CRISPR/Cas9, offer multiple benefits. First, the reduction in the cost and time for the development of new varieties is significant. Estimates suggest development times ranging from 7 to 25 years can be reduced to a span of 2–3, while the cost of editing a gene can be as little as €10 (Friedrichs et al., 2019; Lassoued et al., 2019). Second, yields and traits can be enhanced; sorghum has been edited for yield increases (Gladman et al., 2019) and rice has been edited for increased heat tolerance (Chen et al., 2020). Third, nutritional enhancement and pharmaceutical protein

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production advancements are also possible, such as vitamin E in sweet corn (Xiao et al., 2020) and tomatoes and tobacco as vectors for Covid-19 vaccine production (Norero, 2020; Vavitsas, 2020). Fourth, gene-edited crops contribute to improved food security (Qaim, 2020) and sustainability through increased water-use efficiency (Glowacka et al., 2018).

As climate changes impacts agricultural products, plant breeding needs to ensure it has access to technologies that can rapidly develop new varieties that are better adapted to new climactic conditions. Without timely access to crops with increased drought tolerance, insect resistance and enhance photosynthesis capacity, for example, will result in lower yields as older varieties are incapable of consistent production in the face of increasing abiotic and biotic stresses. Zhang et al. (2017) identify that gene editing is being applied to crops to improve yield, increase disease resistance, provide herbicide tolerance and improved oil and nutrient composition. Eriksson et al. (2019) and Qaim (2020) summarize the various crop varieties and traits of value currently in the commercialization pipeline, including: soybean (drought tolerance, salt tolerance, high oleic acid, low trans-fatty acids), corn (increased starch), potato (lower acrylamide), banana (fungus and virus resistance), cassava (virus resistance) and wheat (mildew resistance, higher fiber).

Regulatory barriers are coming under increasing scrutiny for their impacts on the commercialization of new agricultural technologies and products. The adverse spillover of EU GMO regulations on the adoption of GM crops in African countries has been clearly articulated by Paarlberg (2008), with similar negative impacts expected due to gene-edited varieties being required to be regulated as equivalent to GMOs (Qaim, 2020). Many developing countries base their regulatory approvals in accordance with the EU and as Qaim establishes, the EU's stance that gene-edited crop varieties must be regulated as equivalent to GM varieties, will have an adverse effect on the adoption of gene editing in these countries.

In a survey of plant breeders and federal regulators, Lassoued et al. (2020) found that only 6% of respondents were proponents of process-based regulatory systems, with 59% supporting product-based systems. The experts surveyed were virtually unanimous that process-based regulatory systems are completely unjustifiable. Process-based regulatory systems regulate the process used to create the eventual product and as technologies progress, the original processes used to create products changes, creating inefficiencies in the ability to regulate the new processes. Product-based regulatory systems regulate the final product that is developed, regardless of the process used to create the product, comparing them to previous products and if the there is no significant difference in risk, the products are approved. Lassoued et al. (2020) posit there is an emerging consensus that regulatory processes need to innovate to address the challenges resulting from new technical opportunities, such as with gene editing.

The EU process-based regulatory system has resulted in a regulatory burden on African and other developing countries, regarding the commercialization of GM crops, which appears to be set to extend into the coming decade, given the CJEU 2018 ruling. Gene-edited crops hold significant potential for increase food security and adjusting the changing climates and an efficient regulatory system within the EU would facilitate adoption of these technologies in other countries (Eriksson et al., 2020; Zaidi et al., 2019). Clearly, the EU regulatory system needs to transition to a product-based system to ensure that regulatory burdens are reduced in countries that are far less food secure than Europe. The challenge is, how might this be possible, or is this even possible? The following section discusses this dilemma.

3. Regulatory gridlock for gene editing technologies

As it was for the commercial approval of GM crops, the EU regulatory burden spills over to countries experiencing food insecurity, which to date, shows every sign of continuing to be the case in terms of the regulation of gene editing. Scientists at 117 research facilities within the EU are calling for revisions to the EU regulatory framework for products developed by gene editing (Max Planck Institute for Developmental Biology, 2019). The European Academies Science Advisory Council (2020) identifies that the EU regulatory system needs to be significantly revised to ensure that Europe remains competitive in terms of agricultural and climate change innovation and investment. Given the strong voice of concern and calls for change from the scientific community, is there a cause for optimism?

The EU is in regulatory gridlock regarding the approval of innovative crop varieties. The EU revised its regulatory framework early in the millennium, moving from a system of domestic approvals and GM crop commercialization authorizations to an EU wide risk assessment and approval system. This established the European Food Safety Authority (EFSA) in 2002, resulting in a two-tiered risk assessment process that decoupled the risk assessment phase from the variety approval phase. EFSA is responsible for conducting risk assessments of any GM variety that is submitted for import or production, consistently delivering risk assessments that GM crops are substantially equivalent to conventional, non-GM crops. The gridlock occurs at the second stage, the variety approval stage. Once EFSA completes its risk assessment, this decision is passed to the European Commission's Standing Committee on the Food Chain. This Committee includes a representative from each EU Member State and has the mandate for granting environmental release approvals for GM crops. For approval to be granted, a 'qualified majority' must be achieved (Smart et al., 2016). Within the EU system, a qualified majority vote means that at least 55% of the Member States (15 out of the 27) have to vote in favour of approval and that those Member States voting in favour include 65% of the total EU population. Committee member votes are politically-based, as if they were grounded in science, EFSA's approval would result in the consistent approval for environmental release for GM varieties by the Committee.

This decoupled risk assessment and variety approval system has proven to be virtually inoperable, approving but a single variety for commercial production since 2002. This approval occurred in 2011 and was granted to a GM potato developed by BASF. This variety was never commercialized by BASF as it took 13 years to receive approval and resulted in BASF announcing that it was moving all of its plant biotechnology R&D to North and South America (BASF, 2012). The EU regulatory system is functional in regard to approving GM crops for import as livestock feed, but is a failure in terms of approval for environmental release within the EU.

4. Gene editing regulation: pharma vs Ag

As the globe is gripped in the midst of the Covid-19 pandemic, discussions pertaining to the return to 'normal life', are ultimately based on the development of vaccines capable of providing immunity. In the plethora of media attention on this, responses from scientists on when vaccines can be expected to be widely available, range from 12 to 30 months, meaning that widespread vaccination may not be available until late 2021 or early 2022. Public and private initiatives on development of Covid-19 vaccines are taking place in countries around the globe. Equally vital in Covid-19 research is the push to developed rapid corona virus testing. Many governments have developed isolation reductions based on the ability to ensure a specific number of tests are conducted on either a daily or a weekly basis, such as 20,000 tests per day. A significant advancement in the development of a rapid corona virus test was announced in early May 2020, when the Food and Drug Administration (FDA) in the USA granted emergency use approval to a CRISPR gene-edited technology-based test (Guglielmi, 2020).

The use of gene editing technologies in the development of Covid-19 tests and vaccines in Europe is a central component of the R&D being conducted. As of mid-April 2020, an estimated 86 Covid-19 vaccines were under development within Europe (The Economist, 2020). Many of the technologies being utilized in the development of these vaccines will result in them requiring to be regulated as equivalent to GMOs. Of the 86

vaccines in development, 26 are utilizing protein subunit technology, 14 using RNA technology, 10 using non-replicating recombinant vectors, 7 using replicating recombinant vectors and 6 using DNA technologies (The Economist, 2020). The glaring policy issue for the EU is, will all gene-edited Covid-19 vaccines and corona virus tests have to be regulated as equivalent to GMOs, thus delaying their commercialization by months, if not years?

Within the EU regulatory framework, Directive 2009/41/EC regulates the contained use of genetically modified microorganisms (GMMs), wherein Article 2(a) states, "'micro-organism' means any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture; " and Article 2(c) stating, "'contained use' means any activity in which micro-organisms are genetically modified or in which such GMMs are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment; " (European Parliament, 2009). The 2018 CJEU ruling that gene editing technologies must be regulated as equivalent to GMOs, establishes that gene-edited corona virus tests and Covid-19 vaccines will be required to be regulated as equivalent to GMOs (CJEU, 2018).

Smart et al. (2016) quantified the mean completion time for a regulatory decision in the EU regarding the approval of a GM crop is 1763 days, nearly five years. It is highly doubtful that any European politician would be willing to accept that no Covid-19 vaccines would be available to Europeans until early in 2025. Certainly, the ability to expedite the regulatory approval process for corona virus tests and Covid-19 vaccines exists within the EU, as it does for all governments, but to do so would publicly acknowledge a dilemma regarding the regulation of gene-edited products. If the EU fast-tracks gene-edited Covid-19 vaccines that would contain genetically edited viral material, deviating from EU GMO regulations, then based on scientific merit, there would be no logical reason for gene-edited plants to still be required to be regulated as equivalent to GMOs. Should the application of gene editing technologies to plant agriculture still require regulation as equivalent to GMOs, it publicly confirms that the entire EU framework is politically motivated, not grounded in robust scientific assessment. This is particularly evident as some gene editing technologies, when applied to plant development, do not result in any foreign genetic material being present in the final product.

Process-based regulatory systems, such as the EU's regulatory system for GMOs, when combined with decoupled risk assessment and product approval mandates, results in a total lack of functionality. To protect its citizens, Europe is going to have to find a means of ensuring that any of the gene-edited Covid-19 vaccines presently under development, are available to health care providers as rapidly as is possible. To enable this, changes will be required to Directive 2009/41/EC, that would most likely clarify the application of gene editing technologies such that they would not require regulation as the equivalence of GMOs. However, if Directive 2009/41/EC is revised to facilitate the availability of Covid-19 vaccines developed via gene editing, scientific merit dictates that Directive 2001/18/EC would similarly be revised, clearly articulating that the use of gene editing in the development of plant varieties would not require regulation as equivalence to GMOs. Directive 2001/18/EC is the directive that governs the authorization for environmental release and commercial production of GM crops.

Europeans have been more accepting of drugs that have been developed through genetic modification than they are of crops. An example is the common use of insulin that is developed through the use of genetic modification, which was approved in 1982. In recognition that revision is needed with the EU regulatory system for dealing with Covid-19 vaccines, in July 2020, the EU announced it would derogate some of the regulatory requirements, designed to expedite the development process.

"Some COVID-19 vaccines and treatments already being developed may be defined [as] genetically modified organisms (GMOs) and are thus covered by the relevant EU GMO Directives. As national requirements to assess the environmental risks of clinical trials on medicinal products that contain or consist of GMOs vary considerably across member states, a derogation from these rules is needed to avoid significant delay in developing life-saving vaccines and treatments" (European Parliament, 2020).

This derogation of regulations for the development of Covid-19 drugs and vaccines will benefit all Europeans. There is potential for the public acceptance of regulation derogation of GM drugs to carry over to GM crops, as the percentage of European consumers concerned about GMOs in their foods has dropped from 63% in 2005, to 27% in 2019 (Ichim, 2020). With significantly lower rates of concern, the potential exists to revise the EU regulatory framework, such that gene-edited crops would not be subject to regulation as equivalent to GM crops.

5. Harmonizing EU pharma and Ag gene editing regulations

If the EU approves the use of gene editing technologies for the development of Covid-19 vaccines and corona virus tests, scientific rational dictates that this method of regulation should be similarly allowed for all applications of gene editing technologies. The scientific underpinnings of risk assessment methodologies are such that allowing the use of a technology for one application, would allow the same technology to be used in other applications following the relevant risk assessment. If a thorough risk assessment indicates that the risks of applying gene editing are substantially different from existing technologies, then merit has been scientifically established to warrant different regulatory requirements. However, if thorough risk assessments of gene-edited vaccines and gene-edited crop varieties do not quantify differing degrees of risk, there is no sound basis for applying different regulatory requirements.

With no sound scientific rational for separate regulatory requirements for health and agriculture application of gene editing technologies, two fundamental changes will be required within the EU's regulatory framework. First, the EU will need to abandon its process-based regulatory system and move to a product-based regulatory system that functions efficiently and safely in many other countries. Second, the EU will need to end its decoupled risk assessment and variety approval process for agriculture. Both of these changes will benefit the approval of gene-edited crops in food insecure, developing countries.

While a process-based regulatory system may have some capacity to regulate products of the technologies that are available for application as the point of establishment, science does not stand still, resulting in process-based regulatory systems eventually being incapable of regulating new technologies that evolve from the existing ones. The EU's regulatory system proves this to be the case. With gene editing technologies ability to conduct targeted and controlled mutation, leaving no foreign genetic material, this rate of mutation, will be in many instances, indistinguishable from natural rates of mutation. Tromas and Elena (2010) identify the rate of spontaneous natural mutation in plant RNA ranges from 10^{-6} to 10^{-5} mutations per site and per generation, meaning that the EU regulatory system is going to attempt to regulate laboratory mutated plants that will be no different from, or even less mutated than, the nature rate of gene mutation in plants.

By forcing gene editing technologies that mutate specific genes in a targeted and controlled manner, the EU is attempting to regulate the impossible. Scientists know this, which is why they are calling for a review and revision of the EU regulations on gene editing technologies and also why companies have moved their plant breeding capacities out of the EU. The dramatic need for regulatory revision is perhaps no more clearly articulated than it is in the call by the European Commission's Group of Chief Science Advisors (2019a: 6), who recommended, "**revising the existing GMO Directive to reflect current knowledge and scientific evidence, in particular on gene editing and established techniques of genetic modification.** This should be done **with**

reference to other legislation relevant to food safety and environmental protection." It simply does not get any clearer than this, process-based regulation in the EU has not worked, is not working and will not work in the future.

The Council of the European Union has acknowledged the need to reconsider how the regulation of gene editing technologies is conducted within the EU and to this end, has requested the European Commission to prepare and submit a report by April 2021 that addresses the regulation of novel genomic techniques (European Commission, 2019b). The requested report will include an assessment of how novel genomic techniques can be used in the development of plants, animals and micro-organisms for agriculture, food, industrial and pharmaceutical applications.

The second revision required is to correct the fundamental flaw in the variety approval process that has resulted in GM crop approval decisions not being based upon science, but rather on political preferences. While EFSA has consistently delivered risk assessment determinations that GM crops varieties do not possess risks that differ from conventional crop varieties, the European Commission's Standing Committee on the Food Chain has approved but a single variety in the past decade and a half. The political interference of the Standing Committee on the Food Chain has rendered the science-based risk assessment process meaningless. Risk assessment experts are fully capable of making commercialization decisions for new crop varieties in dozens of other GM crop producing countries and there is no reason to believe that the risk assessment experts employed by EFSA are any less qualified than their international peers.

The current risk assessment methodology that is used to assess the risks of GM crops is underpinned by 1183 peer reviewed publications and government sponsored research reports (Gleim and Smyth, 2018). The EU has conducted risk assessments on GM crops that are allowed to be imported for use as livestock feed, without issue, not to mention that GM corn has been produced in the EU Member States of Portugal and Spain for over 20 years, again without issue. Clearly, science-based risk assessment of GM crops is a thorough process that has approved safe technology for environmental release and commercial production around the world for 25 years. Putting environmental release decisions in the hands of a politically-based committee such as the EU has done, verifies that politics is preventing release, not scientifically confirmed risks.

6. Conclusions

For the past 20 years, European Union regulations have posed as a barrier to the agricultural innovation of GM crops, both within the EU, but also to developing, food insecure African and Asian nations. Current EU regulatory requirements regarding gene editing technologies are poised to remain a burden to improving food security for the foreseeable future. While the negative impacts of the CJEU 2018 ruling have been highlighted by European scientists, the entrenched political opposition to revising the EU regulatory framework make the probability to meaningful revision slim at best.

The EU presently finds itself in the midst of an enormous policy dilemma. The need, and demand, for Covid-19 vaccines and corona virus test kits will be unprecedented, yet the EU regulatory framework will require any vaccines and tests developed through the utilization of gene editing technologies will be required to be regulated as equivalents to GMOs, potentially delaying their approval for commercial release. Certainly, the EU has the ability to fast-track the development of vaccines and tests to address the Covid-19 pandemic, but doing so will create one regulatory stream for gene-edited vaccines and a separate stream for gene-edited plants. With no sound scientific rational for distinct regulatory processes, facilitating the approval of gene-edited vaccines and tests, while forcing gene-edited plants to be regulated as equivalent to GMOs, will result in further investment reductions in agricultural innovation. This regulatory rigidity will adversely impact European farmers as they will have reduced access to innovative crop varieties capable of maintaining high yields through changing climates, as well as spilling over to impact the adoption of gene editing technologies in developing African and Asian countries.

The EU is going to be constrained by its own regulatory system to respond to Covid-19 with gene-edited vaccines and corona virus test kits, given the requirement that any product be regulated as the equivalent to a GM product. The demand to ensure human health and public safety will put relentless pressure on the European Commission to revise the regulatory requirements for gene-edited vaccines and test kits. This provides the EU with the opportunity to abandon its process-based regulatory system and move to a product-based regulatory system. By removing the precautionary focus of the EU regulatory framework and re-establishing it to be based on science, EU governments will be capable of responding in a timely manner regarding the response to Covid-19. With no scientific rational to differentiate between gene editing technology applications for human health and agriculture, a revised regulatory framework would integrate the risk assessment and approval process. Such a move would significantly reduce the regulatory barriers for the development of gene-edited plants.

The EU has a unique and rare opportunity to revise its regulatory system in such a way that frees itself from the shackles posed by environmental and political opposition. Adopting a science-based product regulatory system for gene editing technologies that integrates approval decisions with EFSA would reverse the 20-year trend of declining agricultural R&D investment within the EU. Without such a change, the EU's regulatory burden will continue for agriculture within the EU, as well as for many other countries.

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