Regulatory and Political Challenges of New Breeding Techniques

HOW TO FIND THE RIGHT EU REGULATION FOR GENOME EDITING PRODUCTS.

CATHERINE REGNAULT-ROGER is Professor of Universities Emeritus at the University of Pau and the Adour Countries (E2S), Member of the French Academy of Agriculture and the French National Academy of Pharmacy and Member of the Scientific Committee of the High Council of Biotechnologies.

In November 2020, the Nobel Prize in Chemistry was awarded to Emmanuelle Charpentier and Jennifer Doudna, co-inventors of the CRISPR-Cas, a genome editing technique published in Science 2012, for this major discovery that revolutionized genome modification techniques.

A BIOTECH BREAKTHROUGH REQUIRES NEW REGULATION

The genome modification techniques, developed as early as the 1940s, reproduce in a research laboratory, phenomena which exist naturally They allow us to free ourselves from the vagaries of nature by selecting the changes to be induced. Random mutagenesis and transgenesis, which require heavy experimental manipulations are now taken over by the NBTs (New Breeding Techniques). Some of these new techniques use enzymes, directed nucleases to change the nucleic bases of DNA. They edit the genome. These latest techniques are more powerful because they are more accurate and less expensive. The CRISPR-Cas technique (CRISPR for *Clustered Regularly Interspaced Short Palindromic Repeats*, which involves a guide ribonucleic acid associated with the CAS enzyme), has been called "molecular scissors" to emphasize its accuracy and also "garage biology" to emphasize the ease of implementing it.

The applications of these new genome-editing techniques are multiple and concern human, animal and plant health. The range of applications is wide, from the production of pharmaceutical proteins by plants or human gene therapy to the *Gene drive* associated with CRISPR, against mosquito vectors of tropical infectious diseases (dengue, malaria, chikungunya, zika). Broad perspectives are now opened up in veterinary medicine (African swine fever as example) or to improve animal welfare (by reducing the cold sensitivity of piglets, or creating hornless cows to avoid dehorning, a painful operation). In the field of plant health, numerous patents based on the CRISPR-Cas technique have been filed to control pest insects and diseases or to adapt to climate change (water deficiency, soil salinity)

Today the regulation that must be applied to NBTs is the key question. Should genome-editing products be considered as GMOs and subjected to the same regulations as transgenesis products? There is no unanimous consensus across the world depending on countries' policy. For agricultural products, the consequences in a globalized world where goods circulate will necessarily be important, not only in terms of competition but also for a given country in terms of national agri-food independence.

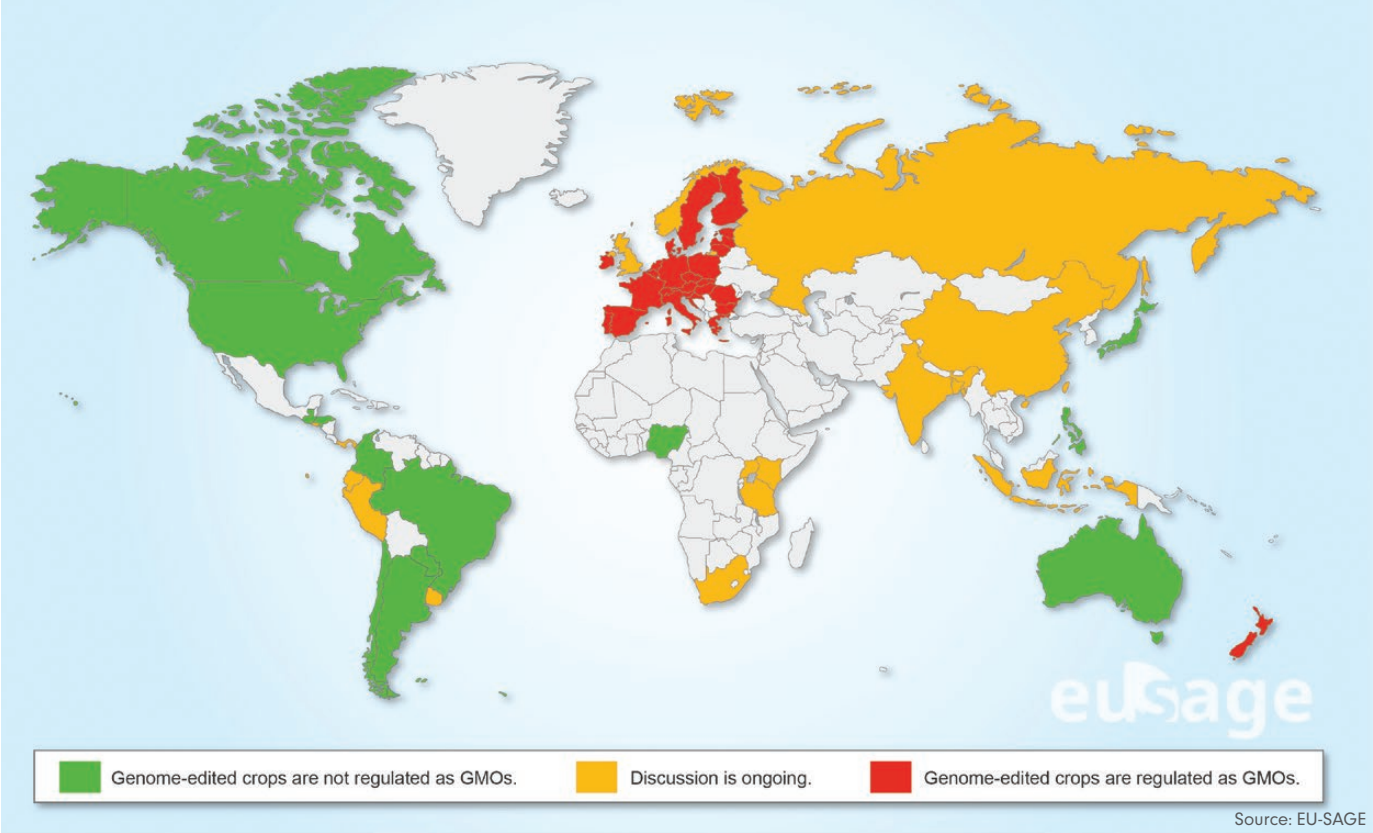
A REGULATED WORLD

Early on, the question arose to examine the risks of the genome changes developed in the laboratory. The Asilomar International Conference was organized in 1975 by Paul Berg (Nobel Prize in Chemistry 1980) to examine the assessment of these risks, and as a result, regulations on the use of biotechnology were put in place in many countries. In the United States, the Coordinated Framework for Regulation of Biotechnology was published in 1986.

In Europe, the implementation of GMO regulations was a multi-step process. It concerns both gene therapies for humans or animals and transgenic crops. European regulations are applied to products obtained by the technique of transgenesis, while those obtained by random (classical) mutagenesis, a technique used since the 1940s, were exempt.

EU-27 GMO REGULATIONS

Two directives articulated together were published in 1989 and 1990, Directives 89/219/EEC and 90/220/EEC "on the use of GMOs in confined or open environments", followed 10 years later, in 2001, by the Directive 2001/18/EC "on the deliberate release into the environment of genetically modified organisms" which is still in force. It was amended in 2015 by the Directive EU 2015/412 "amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory", which is in fact focused on the societal acceptability of transgenesis. Finally, in 2018, the Directive 2018/350/EC "amending Directive 2001/18/EC of the European Parliament and of the Council as regards the environmental risk assessment of genetically modified organisms" updates the regulatory framework for environmental risk assessment. The Regulation (EU) 2015/2283 on novel foods completes these rules and guidelines.



Source: EU-SAGE

This regulation leads to provide extensively documented files, including studies of highly unlikely prospective hypotheses and includes drastic and expensive post-market monitoring to detect an uncertain and unknown anomaly that might be related to the cultivation of a transgenic plant (no hypothesis driven). Only the major international conglomerates in the sector (now the American Corteva, the Chinese ChemChina and the German Bayer), have sufficient financial base to assume such regulatory requirements, which are added to the normal application process for marketing authorisation for a new plant variety.

If it might seem appropriate to have such regulations at a time when there were many unknowns about the behaviour of genetically modified plants in the field, is it still the same today? There are several arguments in favour of its relief. For example, the three American National Academies of Arts and Sciences, Engineering and Medicine published a more than 600-page report in 2016, following the analysis of more than 1000 scientific publications on cultivated plants produced by genetic engineering over a 20-year period and concludes that these biotech plants grown in accordance with good agricultural practices do not present more toxicity and ecotoxicity or environmental risks than conventional plants.

It was in this context that the question of regulations that should be applied to the NBTs has arisen from 2015 onwards.

A DIVIDED WORLD

Since 1996, the year in which the first transgenic crops (biotech) were planted, the world is divided into two parts: on the one hand the countries that adopted them (North and South America, Asia and the Pacific-Oceania region) and on the other hand, those that rejected them (Middle East and a majority of African and European countries, with the exception of Spain and Portugal).

So, this clearly distinguishes probiotech countries (which grow and import GMO crops) and those that are more reserved (which import GMO crops but refuse to grow them). This is further reflected by the rules that are applied for genome editing innovations.

GENOME-EDITING PRODUCTS NON SUBMITTED TO GMO REGULATIONS IN MANY COUNTRIES

It is therefore not unexpected that the first regulations applied to genome-editing products were taken in South America, where countries are often described as the "land of choice" for biotech plants.

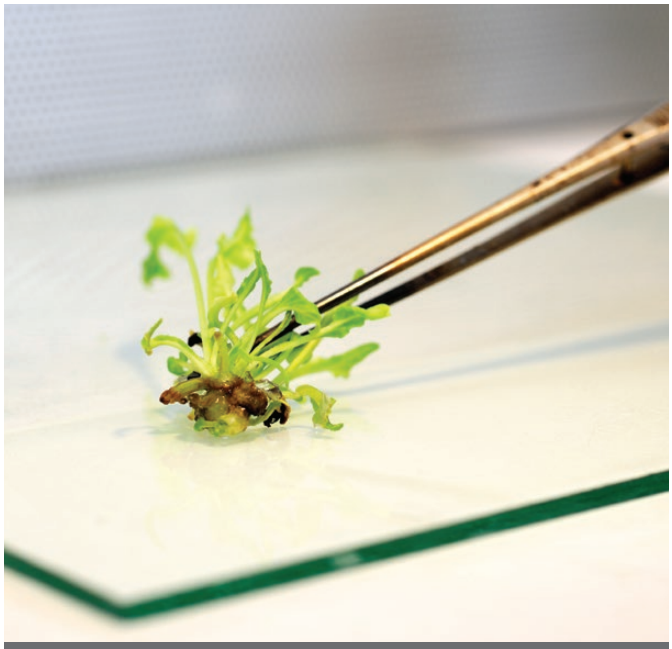
Argentina, Chile, Colombia, Brazil and Paraguay decided to proceed on a case-by-case basis but by exempting from regulation any new organism genetically modified by NBT that would not incorporate "new combinations of genetic material". Genome-editing products that do not incorporate external DNA are not considered GMOs. Presently Uruguay does not have any specific regulations for genome-editing products but has signed a manifesto with 12 other countries in 2018 to the World Trade Organization stating that "arbitrary and unjustified distinctions" between cultures derived from genome-editing or conventional grow-up should be outlawed.

In North America, a new regulation, called the SECURE (Sustainable, Ecological, Consistent, Uniform, Responsible and Efficient) Rule applied to new genome-editing biotechnology, was published on 18 May 2020 in the American Federal Registry after a wide consultation was held to gather the opinion of all. A plant genetically edited for minor changes in the genome such

as changing or removing a pair of bases or introducing a gene known to belong to the plant's genetic pool (SDN-1 and SDN-2) will be exempt from federal regulations applied to GMOs. The USDA-APHIS (Animal and Plant Health Inspection Service) estimates that less of 1% new varieties submitted for marketing authorization will not benefit from this regulatory relief. Canada does not treat genome-editing products differently from other products from innovations that have new traits. What matters are the properties of the finished product obtained, which is assessed on a case-by-case basis by the Canadian Food Inspection Agency (CFIA).

On other continents, Japan and Israel have decided not to regulate genome edited products that do not contain new foreign DNA. Australia exempts SDN1 genome editing products from regulation. In 2020, Russia reaffirmed its opposition to the cultivation and breeding of agricultural GMOs except for research purposes, but since 2019 a research programme of 111 billion roubles (about 1.23 billion euros) has been set up aiming to develop some 30 genetically edited varieties of wheat, barley, sugar beets and potatoes which should be considered equivalent to conventionally obtained varieties. China has not defined a specific regulatory status for genome-editing products but has committed US$10 billion in research programmes. China is also the country which owns the highest number of patents for CRISPR/Cas agricultural applications. India and several countries in Southeast Asia are continuing their assessments. The New Zealand government, following a decision by High Court of this country, ruled in 2016 that genome-editing products should be considered GMOs. But ensuing debates conducted by the Royal Society of New Zealand after this decision, some voices (New Zealand's Opportunity Party) are asking for a de-regulation of gene edited organism with no added new genetic material.

What are the consequences of these regulatory adjustments? In Argentina, which opted early in 2015 for regulatory relief, lower approval costs are accompanied by an expanded supply of new engineering products. This situation is promoting the development of new and more efficient varieties to adapt to climate change or to better resist crop pests and pathogens.



Beet bud created by micropropagation. Source: Florimond Desprez

DEBATE IN THE EUROPEAN UNION

The situation is quite different in the European Union (EU).

Legally seized by the French Council of State (Conseil d'Etat), the European Court of Justice (ECJ) ruled on products obtained by directed mutagenesis (thus in particular obtained by genome editing). By a judgment of 25 July 2018, the Court ruled that the products obtained by mutagenesis techniques post-Directive 2001/18 must be subject to EU GMO regulations, while those obtained by "traditional" mutagenesis techniques (used before 2001) are exempted as previously but Member States are given latitude to submit these "traditionally produced" organisms as well. This judgment was transposed into French law by the Council of State on 7 February 2020 with a very restrictive interpretation. Consequently, the French Council of State calls for herbicide tolerant varieties, which originated from spontaneous mutagenesis in the field but were improved by mutagenesis directed in the laboratory, and already used in the field for several years, be removed from the Official *Catalogue of French cultivated species and varieties*. However, the European Commission, supported by five Member States issued a detailed opinion on 22 September 2020 challenging the conclusions of the French Council of State and asking it to review its decrees. It states that there is no need to distinguish between *in vitro* and *in vivo* or spontaneous mutagenesis, perfectly in line with the opinion of the Scientific Committee of the French High Council of Biotechnologies issued on 29 June 2020, and that the decisions of the French Council of State are, in this case, contrary to European regulations within the framework of the Common Market.

The ECJ ruling was also commented on by the EU Group of Chief Scientific Advisors, members of the Scientific Advice Mechanism. In a statement entitled "A Scientific Perspective on the Regulatory Status of Products Derived from Gene Editing and the Implications for the GMO Directive", the Committee recommended "revising the existing GMO Directive to reflect current knowledge and scientific evidence, in particular on gene editing and established techniques of genetic modification". It calls for the characteristics of the final product to be evaluated instead of legislating from the method of obtaining. It stresses the need to create a regulatory environment conducive to innovation so that "society can benefit from new science and technology."

This debate is now open. A European citizens' initiative Grow scientific progress launched by a group of European students from Wageningen University called for a revision of the Directive 2001/18/EC and a change in existing legislation to "focus on the crop rather than the technique. In this way safety is ensured while the valuable benefits of new techniques are not lost to illogical regulatory hurdles." Political parties are also taking over. Some members of the German Green Party published in June 2020, a manifesto entitled: "New times, new responses: regulating the law of genetic engineering in a modern way". They point out that applied genetic engineering in human health is universally accepted and that applications in agriculture can also be part of sustainability with "appropriate supervision", saving time to face the challenges of the future such as climate public change. In November 2020, the European Union of Agricultural Academies (UEAA) was concerned that 80% of patents filed on the applications of the CRISPR-Cas technique belong to American or Chinese companies as opposed to less than 10% European ones. It takes a stand to call for new regulations on NBTs and GMOs adapted to modern breeding techniques.

It is in this context that the European Commission is currently developing a document planned to be released in early spring 2021. Such a document is of critical importance to the future of European agriculture and the agri-food independence of its Member States.

Editor's Note: This is an abbreviated version of the full article, which you can find on our website www.european-seed.com