Received: 12 July 2021 | Accepted: 4 March 2022

DOI: 10.1002/aepp.13259

FEATURED ARTICLE

EU regulation of genetically modified microorganisms in light of new policy developments: Possible implications for EU bioeconomy investments

Justus Wesseler[1] | **Gijs Kleter**[2] | **Marthe Meulenbroek**[1] | **Kai P. Purnhagen**[3]

[1]Wageningen University, Wageningen, The Netherlands

[2]Wageningen Food Safety Research, Wageningen, The Netherlands

[3]University of Bayreuth, Germany

Correspondence
Justus Wesseler, Wageningen University, Wageningen, The Netherlands.
Email: justus.wesseler@wur.nl

Editor in charge: Stefano Boccaletti

Abstract

Many developments in the bioeconomy depend on the use of genetically modified microorganisms (GMMs). GMMs are used in bioreactors to convert biomass into food, feed, and energy products. The recent judgment by the Court of Justice of the European Union on gene editing technologies has affected the use of GMMs. A heated debate has started on whether and under what circumstances GMMs should be considered genetically modified organisms. This kind of decision is extremely relevant, as it will have a strong effect on the innovation of sustainable supply chains in the bioeconomy. The question has been raised as to whether the regulatory policies on GMMs can be justified from a sustainability perspective and, in particular, whether they do not endanger the European Green Deal, the flagship policy strategy of the new European Commission under Ursula von der Leyen. This contribution will first provide an overview of GMMs and their importance for the development of the bioeconomy, followed by a theoretical framework for assessing investments in GMMs. The third part of the article includes a discussion of

four scenarios for regulating GMMs in the future, derived from the EU legal environment. The potential implications of the scenarios are assessed by linking them with the benefits and costs of investments in GMMs, following a modified version of the model presented in Purnhagen and Wesseler (2019). The results show that reforms based on the current EU legal environment do not look very promising to further support the use of GMMs. This has important implications for reaching the objectives of the Green Deal, as more radical legal changes are needed for the success of the initiative.

KEYWORDS

EU bioeconomy, genetically modified microorganisms, labelling, regulations, sustainability

JEL CLASSIFICATION

Q01, Q16, Q18, K13, K20, K32

Genetically modified microorganisms (GMMs) are widely used in various sectors, including agriculture, pharmaceuticals, environmental pollution control, and various industries, such as food, paper, and textiles, because of their enormous diversity (Liu & Kokare, 2017; Mallikarjuna & Yellamma, 2019; Raveendran et al., 2018). According to Directive 2009/41/EC of the European Parliament and Council on the contained use of GMMs, "a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination" (European Parliament 2009). Their use has been challenged by a judgment of the Court of Justice of the European Union (CJEU) on the use of mutagenesis in plant breeding. The CJEU decided on July 25, 2018, that organisms developed by recently developed gene editing technologies using mutagenesis, such as most CRISPR-Cas, are considered genetically modified organisms (GMOs) and are not exempted from approval for release into the environment or placement of the market, as they do not have a track record as those "*which have conventionally been used in a number of applications and have a long safety record*" (EUR-Lex, 2018, p. 10). The impact of the judgment on plant breeding has been widely discussed in the literature, which highlights the negative implications for developing plants that allow us to better adapt to climate change-related impacts (National Academy of Sciences Leopoldina, Union of German Academies of Sciences and the German Research Foundation, 2019; Purnhagen et al., 2021). Mutagenesis is also widely used for developing GMMs, such as for biological control agents (Frederiks & Wesseler, 2019). Consequently, it can be questioned if the judgment has similar implications as the ones observed for plant breeding. Of relevance are implications for developing products that contribute to the sustainable development of the bioeconomy and for the regulations of those products, including product standards, costs and time length of the approval process, and labeling requirements. Thus far, this has not been extensively discussed in the literature.

In this article, the different uses of GMMs and their economic importance will be discussed, as well as the European Union regulations concerning GMMs and the consequences of CJEU's

judgment. We will start with discussing the sectors where GMMs are or could be used in the production process of food, feed, and nonfood and feed biobased products. A generic model previously used to assess the impact of the CJEU decision on plant breeding will be adopted to assess the impact on GMMs. In the tradition of the writings of Ronald Coase (2007), this is followed by a discussion of possible regulatory approaches and an assessment of the benefits and costs for investment based on the theoretical model presented. We show that solutions based on the existing legal environment and political environment will have limited chances of success, and more radical changes will be needed to stimulate investments in GMMs.

APPLICATIONS OF GMMS

GMMs are increasingly used by pharmaceutical companies in the development of novel products (Parisi & Rodriguez-Cerezo, 2021). Recombinant technology has revolutionized the way that novel vaccines are developed and produced. GMMs can bring immunogenic material (antigens) into human or animal immune systems to induce an immune response. GMM-based technologies could produce novel products against diseases such as malaria, tuberculosis, AIDS, and other emerging diseases (Kauffmann et al., 2019). These new technologies create opportunities for the development of vaccines in various health sectors (Leunda & Pauwels, 2019). Timely response to already known or new epidemics requires the development and manufacturing of vaccines. Vaccination remains the most effective response to controlling pathogens. However, the development of novel vaccines and their deployment in epidemics remains limited. This came to light especially during the 2015 Ebola outbreak (Drury et al., 2019) and the current coronavirus disease 2019 (COVID-19) pandemic (Wesseler & Purnhagen, 2020).

GMMs promote plant health and can increase agricultural production by using fewer chemical products. The technological developments that have occurred in biotechnology, such as the use of CRISPR/Cas for genome editing, have also stimulated new possibilities for the use of GMMs in agriculture (Glandorf, 2019). GMMs can be used for the bioremediation of polluted soils and therefore increase soil productivity. They can also be used as bio-detectors to monitor soil pollution so that it can be managed more efficiently or prevented. Lastly, GMMs can enhance nitrogen fixation and nutrient uptake in the soil (Gosal et al., 2020). Microbial biological control agents (MBCAs) are an example of GMMs that could be used in agricultural practices to make them more environmentally friendly and less polluting. MBCA can be useful for the control of diseases, weeds, or pests in crop plants. Therefore, they may be used as an alternative to plant protection products with a chemical composition (Scheepmaker et al., 2016).

The increasing number of pollutants in the environment is a threat to the ecosystem. Some organic pollutants, such as pesticides, polychlorinated biphenyls (PCBs), and polyaromatic hydrocarbons (PAHs), are resistant to degradation. This is an alarming concern for wildlife as well as humans. Various physiological and biological measures are being used globally to degrade these organic pollutants and improve the quality of the environment. Bioremediation has become the best and most promising strategy for degrading organic and inorganic pollutants (Kumar et al., 2013). Bioremediation is the use of biological processes or the activity of organisms (which are mainly bacteria and fungi) to transform pollutants into inert substances, which renders them nonreactive or inactive in chemical reactions. Bioremediation is currently the cheapest method and is more efficient in removing pollutants than conventional methods (Letti Junior et al., 2018). It is a safe and economically viable alternative compared to other physico-chemical methods. Primarily, microorganisms degrade or transform environmental contaminants into less

toxic or even harmless forms. The use of GMMs has received a lot of attention in bioremediation; however, they are still largely limited to laboratory trials (Gupta & Singh, 2017).

Food enzymes (Fes) are increasingly used in the food industry. Natural FEs more often have limitations in refined and high-intensity food processing conditions (Zhang et al., 2019). The yield of this FE production can be increased by optimizing the fermentation process. This can be carried out by using GMM strains (Deckers et al., 2020). In Europe, an important market sector that uses microorganisms in the processing of food is the dairy industry. Roughly one-third of the milk in the EU is used to extract compounds further processed into food and feed ingredients. Examples of these products are cheese, yogurt, and lactose-free milk products (Zaheer & Gupta, 2019). Genetically modified fungal strains are commonly used to produce FEs in several industries, including the dairy sectors, as they are able to grow on low-cost substrates and they excrete large amounts of enzymes (Deckers et al., 2020). However, yeast and other GMM for extracting compounds from milk are not yet widely used in the EU.

Wastewater caused by the textile industry is seen as one of the worst polluters of water and soil ecologies. Textile wastewater contains, among other substances, persistent coloring pollutants and several heavy metals, such as arsenic, lead, and nickel. Therefore, wastewater requires sufficient treatment before it is discharged to protect public health and the environment. However, there is still no economically viable treatment method to sufficiently treat wastewater. It is a major challenge to develop such a cost-effective and eco-friendly novel technique (Kishor et al., 2021). Microorganisms such as fungi, bacteria, algae, and yeast have been used and examined by various researchers as treatment options for textile industry wastewater. These microorganisms can be used to decolorize, detoxify, degrade, and mineralize a range of wastewater pollutants by leveraging their metabolic pathways and biosorption processes. Microorganisms can also reduce and detoxify various metals in wastewater (Cao et al., 2019; Kumar et al., 2020). The textile industry is one of many industries that could potentially use GMMs to make their products and production processes more sustainable.

Next to these industry-specific examples, GMMs can play a role in the development of a circular economy. The bioeconomy plays an important role in such an economy, as it produces renewable natural resources and converts these resources and waste streams into value-added processes, products, and services (OECD, 2011). The use of GMMs in various industries and biotechnology could ensure more sustainable production and the simultaneous development and growth of the bioeconomy. By using GMMs in the production chain, a wide range of industries could carry out production in a faster and more efficient way compared to the current situation (Bilal & Iqbal, 2019).

GMM REGULATIONS IN THE EU

GMMs are involved in the production processes of many industries, as mentioned above. The release and consumption of products that use GMMs in the production process has raised questions about their safety for human health and the environment. GMMs potentially bear hazards for which data should be provided during risk assessment (EFSA, 2011). Gene products and proteins have the potential to cause toxicity and elicit allergic reactions. Certain, but not all, proteins can be toxins, such as various proteins produced by *Staphylococcus aureus*, that are associated with food poisoning. Therefore, it is important to verify whether newly expressed proteins from a GMM bear resemblance to these and other known toxins. Newly expressed proteins from GMMs are assessed for resemblance to allergenic proteins and are easily digested.

GMMS are also tested for horizontal gene transfer. Horizontal gene transfer is the potential carryover of DNA containing functional genetic sequences from one individual of one species to another individual of a different species. This may impart new properties to the new species, some of which might give it a selective advantage over other microorganisms when they are competing for the same niche. Much attention has been given to antibiotic resistance markers, which are used to select successfully more easily transformed cells shortly after the "event" with the inserted DNA has been formed. The transfer of antibiotic resistance to other microorganisms could compromise the effectiveness of antibiotics. GMMs may have the ability to colonize, for example, the human gastrointestinal tract, and potentially interact with other microbiota, particularly in the gastrointestinal tract. Such exposure may affect the functioning of the normal microbiome.

To ensure that products containing or produced using GMMs are safe, the EU has established different legislative instruments. Before a product can be placed on the market, a scientific risk assessment is required. The European Food Safety Authority (EFSA) GMO Panel has published a guidance document for the risk assessment of GMMs if they are used in food or feed products (EFSA, 2011). The assessment consists of two parts, namely, the characterization of the GMM and the possible effects that the modification might have on the safety of the product itself. The characteristics of the GMM consist of different parts: the parental organism, the donor of the genetic material used, the genetic modification, and the final GMM and its traits. Furthermore, the composition, nutritional value, potential toxicity/allergenicity, and impact of the product on the environment are evaluated. The outcome of this risk assessment then undergoes a scientific evaluation to declare whether it raises safety issues. This evaluation will be used by different European regulatory authorities to decide whether the product should be authorized for commercial use (Aguilera, Gomes, & Olaru, 2013). To illustrate the operation of the legal environment of GMMs in the EU, the following two examples of MBCA and FEs are discussed in more detail.

MBCA can be used in agricultural practices as a replacement for plant protection products with a chemical composition. They contain living microorganisms, such as fungi, viruses, and bacteria. MBCA are regulated at both the EU and Member State levels in the EU. To ensure the management of food and environmental safety risks, these MBCAs need to undergo a comprehensive risk assessment. Directive 91/14/EEC introduced this risk assessment. Regulation 1107/2009 revoked Directive 91/14/EEC and introduced a regulatory environment that better fits the features of MBCAs. Consequently, the total time length for approval is reduced by about 30% but still takes on average more time than in the United States (Frederiks & Wesseler, 2019). The same has been observed for the approval of GMOs. The average time for approval in the EU takes much longer than in Canada, China, or the United States (Jin et al., 2019; Smart et al., 2017). In the current EU GMO legislation, a genetically modified MBCA is defined as a GMO. Therefore, for a genetically modified MBCA, in addition to the risk assessment under Regulation 1107/2009, an environmental risk assessment is required before it can be placed on the market (Scheepmaker et al., 2016). This has limited the application of genetically modified MCBAs.

In the food and feed industry, genetically modified microbial strains are used to produce enzymes, flavorings, and additives. FEs are evaluated worldwide by the Joint FAO/WHO Expert Committee on Food Additives on a voluntary basis and in the EU by the EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavorings, and Processing Aids (CEF Panel). The EU decided to harmonize regulations related to the commercialization of FE and established two regulations. The regulations settle a common authorization procedure for FE, food additives,

and flavoring and harmonize the rules on the use of enzymes in food. Further, they require a submission of applications to have these FE, food additives, and flavoring authorized. The quality control of FE preparations already on the market is under the responsibility of the manufacturers. This holds true for both the EU and the rest of the world (Deckers et al., 2020).

When genetically modified enzymes are used to produce food, which are, however, not part of the final product (i.e., a processing aid), this enzyme is not subject to specific EU GMO regulations and hence does not require labeling. The rules for labeling established under Regulation (EC) No 1829/2003 are summarized in Table 1.

Regulation (EC) No 1829/2003 only applies to food and feed that consist of, contain, or are produced "from" a GMO but not if they are produced "with" a GMO. The reasons for this are two-fold, as clarified in the GM Food and Feed Regulation, that is, Regulation (EU) No. 1829/2003, (1) processing aids that are only used during the production process are not covered by the definition of food and feed and (2) neither are food and feed manufactured with the aid of these enzymes included within the scope of the GM Food and Feed Regulation and hence, do not need to be labeled.

The regulation made this caveat specifically for certain enzymes, leaving the question of other products produced with GMMs open. The response came from the European Commission, which clarified in 2004 (and reaffirmed in 2019) that the use of fermentation by GMMs under contained conditions for the production of food and feed ingredients (e.g., vitamins, flavorings, additives) but without (parts of) the GMM, such as its DNA occurring in the final product, also qualifies as "produced with" a GMM (European Commission, 2004, 2019). Accordingly, no separate parallel application for market approval needs to be filed under the GMO regulations. However, the applicant will still have to address the safety of GMM in their application dossier for the specific category of product (e.g., feed additive) and prove the absence of viable or dead cells or DNA of the GMM from the product.

Therefore, it must be determined whether genetically modified source material is present in the food and feed. This indicates that when a GMM is used as an aid in the processing of the food and feed, it does not fall under the Directive 2001/18/EC for release into the environment, and therefore, GMO labeling is not required either. If the GMM is not removed from the FE,

TABLE 1 Labeling requirements for genetically modified (GM) products

GM products	Example	Labeling requirement
GM plants, seeds, and food	Maize, maize seed, cotton seed, soybean sprouts, tomato	Yes
Food produced from GMOs	Maize flour, soybean oil, rape seed oil	Yes
Food additive/flavoring produced from GMOs	Highly filtered lecithin extracted from GM soybeans	Yes
GM feed	Maize	Yes
Feed produced from a GMO	Corn gluten feed, soybean meal	Yes
Feed additive produced from a GMO	Vitamin B2	Yes
Food from animals fed on GM feed	Eggs, meat, milk	No
Food produced with the help of a GM enzyme	Bakery products produced with the help of amylase	No

Abbreviation: GMO, genetically modified organisms.
Source: Modified from the European Communities (2003).

labeling is required. It is therefore important to know whether an FE is used as an additive or ingredient and may have to be labeled or as a processing aid and therefore does not need to be labeled (European Commission 2014).

Table 2 shows the regulatory environments of GMOs, GMMs, and living modified organisms. The European Commission recently resolved the uncertainty surrounding the regulatory status of new genome editing techniques being applied to GMMs under Directive 2009/41/EC (National Academy of Sciences Leopoldina, Union of German Academies of Sciences and the German Research Foundation, 2019), indicating that microorganisms developed with these techniques indeed have to be considered GMMs subject to the provisions of GMO legislation, particularly Directive 2009/41/EC, for their use in containment, and Directive 2001/18/EC, if they are released into the environment or placed into the market (European Commission, 2021, p. 21).

Development of microbial biotechnology beyond the EU

In the United States, the Coordinated Framework for Regulation of Biotechnology was issued in 1986, which concluded that no new statutory authorities were necessary to regulate biotechnology products. In the framework, a division was made for agencies involved with agricultural, food, and pesticidal products. They include the US Food and Drug Administration (FDA), the US Department of Agriculture (USDA), and the Environmental Protection Agency (EPA). The USDA Animal Plant Health Inspection Service regulates microbes plant pests under the National Environmental Policy and Plant Protection Act. GMMs and other genetically engineered constructs are regulated by the EPA and subject to the Federal Food Drug and Cosmetic Act under FDA and the Federal Insecticide Fungicide and Rodenticide Act under EPA. GMMs used as bioremediation agents and biofertilizers and for producing various industrial compounds, such as biofuels, are also regulated by the EPA under the Toxic Substances Control Act (Wozniak et al., 2012). This differs from the regulatory environment in the EU, where all GMMs are regulated under the same directive.

The use of genetic modification of microorganisms in the food and feed industry has already been proven to be important in the past, as several traditional genetic modification techniques

TABLE 2 Ordinary least squares (OLS) regression results of the Monte Carlo simulation

Variable	Coefficients	*t* Stat
Intercept	6.7640 (0.0197)	342.4964***
κ_1 (R&D phase)	0.7091 (0.0017)	420.9326***
κ_2 (approval phase)	0.7375 (0.0017)	437.4946***
κ_3 (ex-post liability)	−0.0134 (0.0017)	−7.9767***
μ (discount rate)	32.1754 (0.1520)	211.6686***
q (probability benefits high)	−15.4388 (0.0151)	−1019.4632***
Observations	120,012	
R square	0.9238	
F-value	291060***	

***Indicates statistical significance at the 1% level and numbers in brackets the SEs.

have been used. However, these traditional techniques have several limitations and are therefore only used for the selection of model and industrial microbial stains, especially in microorganisms such as algae and fungi. New genetic modification techniques have promising applications in the food and feed industry, as they produce improved microbial strains with greater speed and ease (Soreanu et al., 2018). These new techniques will also be used for modifying the genome of traditional microbial strains, such as beer and wine yeast, with which food and feed products are produced or made.

The research and application of these new genome modification techniques have received worldwide attention. Several research groups in the United States, Brazil, and Belgium have used the CRISPR-Cas9 technique to genetically modify yeasts to modify the flavor profile of beer and to enhance flavor and aroma production. One of the yeasts used in this method produces aromatic molecules that are similar to the molecules found in hops. This offers a more sustainable brewing method, as there is no longer a need to add hops (Denby et al., 2018). This genetically modified yeast (*Saccharomyces cerevisiae*) is used by multiple breweries across the United States (Mertens et al., 2019), while various other GM yeast strains have followed suit.

Another application of the new genome modification techniques is the white button mushroom. This mushroom is one of the two GMMs that has received a regulatory declaration in the United States. This modification prevents mushrooms from turning brown. This increases their shelf-life and reduces food waste. The mushroom received clearance in the United States by the USDA in 2016. However, the mushrooms are not yet commercialized (Mathur, 2018; Waltz, 2016).

ECONOMIC MODEL ASSESSING INVESTMENTS IN GMMs

As is the case for other GMOs, GMMs can be regulated at different levels in the EU. Primary law, in particular, the rules on the free movement of goods and the environment, sets out a general framework for the regulation of the GMO market. Several acts of secondary legislation such as Directive 2001/18/EC cover sector-specific situations. Such legislation at the secondary level can be designed using different harmonization methods, especially when it comes to choosing between minimum and maximum harmonization or a combination of both. Minimum harmonization is understood as providing a minimum level of protection in secondary legislation but does not preclude member states from providing a higher level of protection, while under maximum harmonization member state may not deviate from the protective level set at the union level (Purnhagen, 2014). These options of minimum and maximum harmonization have different economic implications. The decision that is made about the level of harmonization is not only important on its own but is mutually conditional with both law-making and the contents of rules to ensure social welfare (Gomez & Ganuza, 2011).

The optimal regulation of new technologies and their implications for social welfare have been widely discussed in the economic literature. Regulatory policy can have several objectives, but there is general agreement in the literature that the main objective is to reduce harm to the society. Economists have a straight answer to the question of the right level of regulations: "*From an efficiency standpoint, the answer to this question is simple: regulate until the incremental benefits from regulation are just off-set by the incremental costs*." (Arrow et al., 1996). As Shleifer (2010), among others, has pointed out, if courts would work effectively, the regulation of a new technology could be solved efficiently by ex-post liability. Ex-post liabilities provide an economic incentive for producers of goods to find measures to reduce the harm they would be held liable for (Shavell, 1984). Holding producers liable also reduces the information problem,

as individuals have, more often than not, better knowledge about their possibilities to reduce the harm than the regulator.

The empirical evidence shows that perfectly working courts are hardly the case. Judges face the problem of imperfect information, for example, identifying who has caused the harm; clients have different amounts of resources available, and some can hire better lawyers than others, the "deep pocket" argument, and offenders may not be able to pay for the harm done and file for bankruptcy (Shleifer, 2010). This gives rise to ex-ante regulatory policies imposed on firms to follow for the provision of goods under question, and the question emerges of the right balance between ex-ante regulatory policies and ex-post liabilities (Kolstad et al., 1990; Shavell, 1984).

The economic implications are a result of the different costs and benefits that firms face under different ex-ante regulatory policies and ex-post liability rules. In general, it holds that the lower the fixed-cost effects of the regulatory policies, the more possibilities firms have to enter a certain sector, and the more competition there will be if new ideas emerge. In general, the more firms involved, the better this will be for the economy in question.

The objective of a firm that is considering investing in a new technology that uses GMMs can be modeled by maximizing the real option value of the investment. In this case, a trade-off results between the ex-ante regulations that a firm has to follow and the related costs, and the ex-post liability costs they may face. Here, ex-ante regulations refer to the additional costs related to bringing to the market a product derived from or containing a GMM in comparison to a similar product that would not be classified as a GMM product. The costs include additional research and development costs, such as additional safety standards that apply to research facilities, including additional training of staff, the generation and delivery of data for risk assessment, and so on. They also include the additional costs related to the approval for release into the environment, if required, and the approval for processing and market release, which require the submission of dossiers to the competent authority responsible for handling applications. These costs can be substantial. Case studies for the approval of GMOs indicate that the costs can be several million dollars for a single event (Kalaitzandonakes et al., 2007). In addition to the direct costs for research and development for approval, the indirect costs that delay the GMM market access need to be considered.

To start with, we apply the model by Purnhagen and Wesseler (2019) for investment in plant breeding, resulting in GMOs to GMMs. The model consists of several elements. F denotes the value of the option to invest. To develop a new technology, firms have to invest in research and development (**R**) and pay for approval (**A**) before reaping the benefits of selling their products on the market (**B**) while facing possible ex-post liabilities (**Θ**). The costs for the research and development investment, R, have to be paid at the beginning of the research phase. Further, annual research and development costs are made, r_t, where t indicates time. The time needed to conduct research and development is not known in advance and, hence, uncertain, and may differ between industries, but expectations exist. The random variable $\kappa_1 \in (0, \infty)$ denotes the time length for research and development. κ_1 follows the exponential failure function $g(k_1) = h_1 e^{-h_1 k_1}$ with a constant failure rate h_1 with $E(k_1) = \int_0^\infty \kappa_1 h_1 e^{-h_1 k_1}\, d\kappa_1 = \frac{1}{h_1}$, derived using the general equation for the expected value of a random variable $x \geq 0$, $E(x) = \int_0^\infty x f(x)\, dx$. In the literature, $g(\kappa_1)$ is also called a survival function, where h is called the constant hazard rate. For further details, see Cox and Oakes (1984) or Pinsky and Karlin (2011).

The intuitive similarity of the uncertain time length for research and development to a failure function is that a failure function indicates how likely it is that, for example, a machine like a car that has survived until today will break down the next day, next month, or next year. The older the car will be, the higher the probability of a break down. The probabilities can be

estimated using data from car insurance companies or other sources. Similarly, for research considering the current state of knowledge, the question would be how likely it is that a new product will be developed within the next or next 2 years? In the case of research, it is of course not a failure, but a success. A value of a failure rate h_1 of 0.1, for example, indicates an expected value for κ_1 of 10 years.

A similar reasoning is applied to the approval process. An application for approval is submitted at the end of the research and development phase at κ_1. This submission includes approval costs **A**. Some of the approval costs are considered to be sunk costs A. Moreover, there are some annual reversible costs, a_t. As with the time necessary for the research, the exact time length of the approval is not known, but expectations exist. This time length until approval is denoted by the random variable κ_2. At $\kappa_1 + \kappa_2$, the product has an approval for entering the market, which generates an annual net-benefit stream denoted by b_t. This is expressed in net-present-value terms B_t at time $\kappa_1 + \kappa_2$. If a product has entered the market and damages or negative information linked to the product occur, the firm may encounter ex-post tort liability and/or reputation costs θ. This possible occurrence of damage is modeled by the random variable $\kappa_1 + \kappa_2 + \kappa_3$. While time is treated continuously, states are treated as discrete variables. Please note that the different time periods overlap.

We consider two future states: one in which the benefits are high, B_h, with probability q, and the other in which the benefits are low, B_l, with probability $1 - q$. The benefits and costs are defined as follows:

Definitions:

$$\mathbf{R}, \mathbf{A}, \mathbf{B}, \Theta \in \mathbb{R}^+ \tag{1}$$

$$\mathbf{R} : = R_t + \int_0^{\kappa_1} r_t e^{-\mu t} dt, \text{ with } r_t \text{ the annuity of annual research and development costs} \tag{2}$$

$$\mathbf{A} : = A_t + \int_{\kappa_1}^{\kappa_1+\kappa_2} a_t e^{-\mu t} dt, \text{ with } a_t \text{ the annuity of annual approval costs} \tag{3}$$

$$\mathbf{B} : = B_t = \int_{\kappa_1+\kappa_2}^{\kappa_1+\kappa_2+\kappa_3} b_t e^{-\mu t} dt, \text{ with } bt \text{ the annuity of annual net-benefits} \tag{4}$$

$$\Theta : = f(\theta) e^{-\mu(\kappa_1+\kappa_2+\kappa_3)} \text{ with } f(\theta) = \begin{cases} \theta, \text{ liable} \\ 0, \text{ not liable} \end{cases} \tag{5}$$

Solving this model by assuming complete capital markets and the possibility that firms can postpone their investment results in the following for the benefits, B_0, needed for immediate investment (Purnhagen & Wesseler, 2019):

$$B_0 > (1 - qe^{-ut}) \left(R \frac{(\mu + h_1)(\mu + h_2)}{h_1 h_2} + \frac{r(\mu + h_2)}{h_1 h_2} + \frac{A(\mu + h_2)}{h_2} + \frac{a}{h_2} + \frac{\theta h_3}{(\mu + h_3)} \right) + qe^{-ut} B_h, \tag{6}$$

with h_i the hazard rate of the respective hazard rate function. B_l is dropping from Equation (6) as it defines values that will always lead to a noninvestment decision.[1] As a delay allows to observe the level of benefits, and if the benefits are low, it does not pay for investing in developing the GMM. The implicit assumption made is that B_l is always that low, that investment would not pay. As over time, new information with respect to benefits arrive, waiting allows to avoid the losses in case benefits are low as illustrated in the seminal paper by Arrow and Fisher (1974). The problem addressed here has been formulated as a discrete-time, discrete-state model. One can immediately think of a continuous time, continuous state version. This substantially complicates the analysis and interpretation of results (Wesseler & Zhao, 2019) and does often not provide additional insights that are of importance for assessing real options (Balikcioglu et al., 2011), while for financial options, this might be different.

As we are mainly interested in the impact in the change of the time length for R&D, approval, and appearance of ex-post liability, we normalize all costs to one.[2] The underlying simplifying assumption made is that stakeholders care about the time-length as mentioned in the introduction. This is further justified by the observation that policy makers can in particular influence the time length (Frederiks & Wesseler, 2019) and that this has received policy attention at EU level under the "*Better Regulation*" agenda. If all costs are normalized to 1, the hurdle rate, or the minimum required additional benefits for one unit of additional investments, yields[3]:

$$(1-qe^{-ut})\frac{(\mu+h_1)(\mu+h_2)(\mu+h_3)+[(\mu+h_2)(\mu+h_3)](1+h_1)+h_1(\mu+h_3)+h_1h_2h_3}{h_1h_2(\mu+h_3)} \quad (7)$$

One important aspect needs to be mentioned with respect to the benefits of the investment. An increase in benefits increases B_0 as well as B_h. If the effect, *c.p.*, is stronger on B_h than on B_0, delaying investment will be more likely and especially if B_0 in Equation (6) is less than the right-hand-side and is similar to an increase in returns to scale in a neo-classical production function. As it is not optimal to use inputs in the range of the production function where there are returns to scale, it is not optimal to invest if there are returns to scale with respect to postponing the investment decision.

A similar interpretation can be applied in the case of new plant breeding technologies that fall under GMO regulations, as provided by Purnhagen and Wesseler (2019). The authors examined the marginal effects of specific parameter values. They identified large marginal effects for reasonable parameter values. Still, an interpretation is difficult as a look at Equations (6) and (7) indicates. Nevertheless, the ratio in Equation (7) is obviously larger than 1 for reasonable parameter values (see also the supplementary information Excel file), where the time length for research and development, approval, and marketing are more than 1 year and hence $h_i < 1$. Equation (6) shows the effect of R&D costs, R and r, approval costs, A and a, and liability, θ, on the hurdle rate. The R&D and the approval costs are multiplied with ratios larger than 1 and the liability with a ratio less than 1 as long as the time length for $\kappa_i > 1$ and the discount rates $\mu > 0$ positive. Keeping this and the earlier assumptions in mind, the effect of a marginal change in R&D fixed costs, R, has the largest impact followed by annual R&D costs, r, fixed approval costs A, annual approval costs, a, and liability, θ.

Purnhagen and Wesseler (2019) did not assess the marginal average effects of changes in κ_i. This can be done using a Monte Carlo simulation. The average effect on the hurdle rate can be estimated using uniform distributions for κ_i ranging between 0 and 10 years; for the discount

rate, ranging between 0% and 10%; for the risk parameter q, ranging between]0,1[; and applying standard OLS regression.

We performed these analyses by running 120,012 simulations. We estimated the following multiple linear equation:

$$\text{hurdle rate}_j = a + \beta_1 \kappa_{1j} + \beta_2 \kappa_{2j} + \beta_3 \kappa_{3j} + \beta_4 \mu_j + \beta_5 q_j + \varepsilon_j, \quad (8)$$

with $j = 1, ..., 120,012$, ε_j the random errors, and the other variables as described above.

The results of the regression analysis, including the summary statistics, are presented in Table 2. The coefficients for research, κ_i, indicate that, on average, a 1-year increase in R&D increases the hurdle rate by about 0.71; for the approval time, the coefficient shows an increase of about 0.74, whereas an increase in the benefits by 1 year reduces hurdle rate on average by a factor of 0.01. The average effect of an increase in the discount rate by 1% increases the hurdle rate by a factor of 0.32. An increase in the probability of benefits being high by a factor of 0.1 decreases the hurdle rate, on average, by a factor of 1.54. Additional results provided in supplementary information further show that by using a stepwise regression approach, adding discount rate and adding the level of uncertainty has no substantial effect on the coefficient estimated for κ_i. The average effect remains the same for the above-mentioned ranges for the discount rate and the uncertainty parameter.

This does not imply that the effect of a change in the discount rate is linear. A sensitivity analysis assessing the results for κ_i at different discount rates for values of 0.01, 0.02, 0.04, 0.06, 0.08, and 0.10 and q fixed at a value of 0.50 shows that κ_1 increases from 0.54 to 0.93, that κ_2 increases from 0.54 to 0.99, and that κ_3 decreases from -0.005 to -0.024. Hence, there is an interaction effect. If the discount rate is high, the hurdle rate effect of changes in R&D and approval costs and in market access is higher (see the sheet "statistics kappa" in supplementary information Excel file).

The model and the results will be used in the following sections to discuss the implications of regulatory options for the approval of GMMs.

ASSESSING DIFFERENT REGULATIVE OPTIONS

We have established above an economic model that assesses investments in GMMs. Differences between regulatory environments can have a significant effect on the outcome of the model. In 2018, the ECJ indicated that organisms developed by new gene editing technologies would be considered a GMO within the scope of Directive 2001/18/EC (EUR-Lex, 2018). However, some exemptions existed for GMO on the market before the Directive was introduced. This exemption was interested by the Court in paras 80, 81 as not precluding Member States introducing more protective national regulations, classifying the exemption as "minimum harmonization."

Whether or not this exemption and interpretation of the policies would also apply to food and feed derived from GMOs was left open by the Court. This exemption from GMO regulation could therefore also apply to the use of GMMs in food and feed production or in other sectors. Directive 2009/41/EC shows the uncertainty of determining whether a certain technique is using GMMs and would be considered a GMO. What is called traditional breeding and traditional mutagenesis breeding is excluded from the scope of Directive 2009/41/EC. For genome-edited organisms, it is uncertain whether they should be classified as GMMs (National Academy

of Sciences Leopoldina, Union of German Academies of Sciences and the German Research Foundation, 2019, Table 2). If these cases do not fall under Directive 2009/41/EU, it is important to know how the development of these techniques is overseen, as this has implications for the return on investments in GMMs. At least four options can be foreseen. They have been summarized in Table 3, including the implications for model parameters presented in Economic Model Assessing Investments in GMMs section. The effects on benefits are discussed under the reasonable assumption of having a stronger effect on B_0 than on B_h as discussed in Economic Model Assessing Investments in GMMs section.

The implications are assessed with respect to an approval process that treats GMMs as not different from other food products that receive approval for use in the entire EU and serves as the reference.

Option 1: GMMs are regulated at the EU level (reference option)

Under this option, GMMs are not exempt from GMO law, and the GMO Directive will apply. This also means that the steps that must be taken to obtain approval apply. A risk assessment has to be undertaken to assess the safety of the product, followed by voting by Member States in the relevant committees. Decisions are reached by majority voting. Taking past cases into account regarding the approval of GMOs, reaching a qualified majority in favor of or against a new technology is highly unlikely (Smart et al., 2015). The European Commission makes the final decision and usually follows the advice of different authorities, such as the European Food Safety Authority (EFSA) and the European Medicines Agency. This decision-making process is highly time-consuming (Frederiks & Wesseler, 2019; Smart et al., 2017). Therefore, the expected approval length (κ_2) will be relatively high, increasing the hurdle rate and decreasing incentives for immediate investment. The market size for products approved will be the whole of the EU. The probability of being held liable will be reduced as the products have passed an EU risk assessment acknowledged by all Member States. Products need to be labeled, and a tracking and tracing system needs to be in place. This increases the possibility of liability in cases where traces appear in unlabeled products. The mandatory labeling requirement for food products will act as a stumbling block for market entry, in light of the experiences with GMO-labeled food products in the EU retail sector (Wesseler, 2014).

Option 2: EU develops a general legislative framework but Member States are free how to apply the framework

In this case, the EU develops a general legislative framework that must be voted on by the EU Parliament and the EU Council. As it is a framework, Member States have the freedom to decide how to apply it to their national legislation. This option can be compared to the EU's General Food Law. Here, the EFSA gives scientific advice and assesses potential risks. However, business operators bear the main responsibility of ensuring that only safe products are placed on the market. Member States are responsible for inspecting that these business operators fulfill the requirements of the Food Law (European Parliamentary Research Service, 2017). For GMMs, this would mean that the way Member States deal with the general legislative framework differs. Some Member States will have strict policies, which could mean a ban on GMMs, while others apply less strict policies with almost no effect on the investment

TABLE 3 Harmonization options and potential impact on the incentive to invest

Option	R&D	Approval	Market	Ex-post liability
(1) New GMMs are regulated at EU level	High. More information for compliance to be developed, including unique identification. This resulted in a high κ_1 value.	Lengthy and costly, a	EU market	Medium, because of EU wide approval, but unapproved events may appear in supply chains.
Model values	High value of R, r_t, and κ_1	High value of A, a_t, and κ_2	High value of B	Medium value of θ and low value of κ_3
(2) EU develops a general legislative framework but MS are free how to apply the framework	Low in some MS and in high in other; incentive to invest in MS with less stringent regulation.	Low in some MS and high in other; incentive to invest in MS with less stringent regulation.	EU market, but with possible limitations depending on MS regulation.	Medium, because of approval, but unapproved events may appear in supply chains.
Model values	Medium value of R, r_t, and κ_1	Medium value of A, a_t, and κ_2	Medium value of B	Medium-high value of θ and low value of κ_3
(3) GMMs will be exempted from GMO law and regulations at Member States level apply	Almost no additional R&D costs resulting in a low κ_1 value.		EU market	Low, because chances of not approved GMMs entering the market low
Model values	Low value of R, r_t, and κ_1	Low value of A, a_t, and κ_2	Medium to high value of B	Low value of θ and high value of κ_3
(4) GMMs are considered as GMOs but exempted from GMO law. Member States take action and are free to implement additional regulations.	Almost no additional R&D costs	Almost no additional approval costs	EU market, but restrictions may apply	Low, because of exemptions
Model values	Low value of R, r_t, and κ_1	Low value of R, r_t, and κ_1	Medium to high value of B	Low value of θ and high value of κ_3

Note: The implications are assessed with respect to an approval process that treats GMMs as not different from other food products that receive approval for use in the entire EU and serves as the reference.
Abbreviations: GMM, genetically modified microorganism; GMOs, genetically modified organisms; MS, European Union Member States.

decisions of GMMs in comparison to approval under the novel food regulation. At the individual Member State level, the costs for R&D and approval can be expected to be lower. The market will be limited to the respective Member States, but products can be sold to other markets after they have received approval from the competent authority in the other Member States. Investors can choose which markets they will target, depending on the restrictiveness of the approval requirements and costs. The market size in this case will be smaller than under Option 1 but labeling would perhaps not be required, depending on the Member State. This reduces the costs of tracking and tracing. Investors can choose the market they want to serve and avoid markets where labeling is required. Option 2 is also close to the regulatory system for GMMs in the United States, where at national level an assessment will be done, but business operators face strong liability rules and Federal States have some degree of freedom implementing national law as, for example, indicated with respect to GMO food labelling (Bovay & Alston, 2018).

Option 3: GMMs will be exempted from GMO law and regulations at Member States level apply

In this option, products that are produced using GMMs are exempted from GMO law and will be treated as "conventional" products. If new products are developed, they will need to be registered. The laws and regulations for these new products at the Member State level apply. If this would be the case, the benefits B will be larger, and both κ_1 and κ_2 as well as A and a_t will be lower. The field trials of GMOs and the corresponding fencing and other compliance costs will not apply. Thus, the research costs R and r_t will be lower. If there were zero additional approval costs ($A = 0$ and $a_t = 0$), the hurdle rate would substantially decrease. In comparison to Option 2, the costs for R&D can be expected to be the same. The markets can be expected to be larger, as the other Member States have to list the products. This is somewhat similar to the market for "conventional" seeds, where Member States require different levels of information from suppliers before entering the respective market.

Option 4: GMMs are considered GMOs but exempted from GMO law: Member States take action and are free to implement additional regulations

In this case, GMMs are considered GMOs but exempted from GMO law at the EU level. However, Member States are able to implement additional regulations. This means that some Member States can more heavily regulate the use of GMMs than others. It is expected that this view among Member States differs, as is the case for GM crops (Smart et al., 2015). This difference can also be seen in the results of Member States at the Standing and Appeal Committee on GMOs. The countries that might be in favor of and countries against the use of GMOs and therefore of GMMs as well can be distinguished. This difference in view among Member States will have implications for the trade in products derived by using GMMs. The benefits B will reduce, as the technology and products cannot be widely used. Moreover, several applications need to be prepared, as Member States are free to implement additional regulations, and therefore A and a_t are expected to increase.

DISCUSSION AND CONCLUSION

We have assessed the impact of changes in the time length for R&D, approval, and appearance of ex-post liability by developing discrete time, discrete state real option model that explicitly includes uncertainty with respect to the time lengths. A simplifying assumption has been made with respect to the costs where, ceteris paribus on the cost sizes, potential investors only look at the differences in time length. This allowed us to simplify the analysis and to generate via Monte-Carlo simulation the impact of changes in the expected time length on the investment hurdle. The effects are substantial. According to our results, a 5-year delay will result in an average hurdle rate of about seven. This substantially reduces the attractiveness of investing in GMMs in the EU market.

The high hurdle rates with respect to time also illustrate the high benefits for policies that reduce the time length of R&D and the approval process. Providing easy access to GMMs and GMM technology for further improvements can reduce the R&D time length. This includes public investments in human capital via university education and/or simplified access to knowledge protected by intellectual property rights. One example is providing free access to technologies protected by patents, as announced by Wageningen University in 2021.

The time length for the approval process can be reduced via harmonization of approval standards for safety assessments. The possibility for almost zero additional approval costs exists as well, if GMM-based food products are treated as other "conventional" food products. The first products that entered the European market using GMM technologies were bakery and cheese products developed using the enzymes produced by GMMs and serve as examples (Tramper & Zhu, 2011).

Nevertheless, changing the current regulatory status of GMMs will be difficult. A change will require that MSs agree on changes with at least a qualified majority. We do not find support based on experiences with earlier attempts on changing GMO regulations with the expectation that this will provide opportunities for approval of GMOs for release into the environment. The legal analysis shows that new GMMs would fall under regulations for GMOs if they were linked to a release into the environment or introduced to the market. Many of the new developments, particularly those linked to strengthening the circular bioeconomy, can be considered to be released into the environment in one way or another. These often include higher-level bioeconomy value chains that follow a cascading strategy. GMMs have high potential for the dairy processing sector. Roughly one-third of the milk produced in the EU is subjected to the extraction of compounds further processed into food and feed ingredients. These compounds can also be produced by yeast cells or other microorganisms. Industry experts expect large-scale production within the next 5 years to happen outside the EU. Whether the EU will contribute to this large-scale production depends on the regulatory environment. If the GMMs being used in the production process must follow the approval process for GMOs, access will be delayed by about three to 5 years, based on the experience made with GMOs.

The regulation of R&D and the approval of GMMs have wider implications for the sustainable development of the EU. The European Green Deal is one of the flagship programs of the new commission. To reach these objectives, technical change will be needed to use natural resources more efficiently, including the substitution of fossil fuels. The bioeconomy, and in particular, the conversion of biomass into nonfood and nonfeed products, is one of the important factors contributing to achieving the European Green Deal objectives. The efficiency of converting biomass on a larger scale depends on the efficiency of the bioreactor converting the biomass, and the efficiency of the bioreactor depends on the microorganisms performing the

conversion. New developments in biotechnology have substantially contributed to increasing the efficiency of the bioreactor. Some of these developments include GMMs. Depending on the use and the production process, those GMMs may be considered in the EU from a legal perspective as a GMO. If those GMMs are considered a GMO, the costs of developing and using those GMMs will substantially increase and even may become prohibitively high. The political economy of such new technologies indicates that those who might lose will attempt to delay their introduction. A delay comes at a high environmental cost and may also endanger the objectives of the European Green Deal. Policymakers must take this into consideration if they wish to achieve their objectives. As dairy farmers in particular will be affected first, policymakers may want to pay attention to this group.

The regulatory environment in the EU will have an effect on the willingness of companies in different sectors to invest in techniques that use GMMs. Considering the different policy options, minimum harmonization will provide stronger incentives for companies than maximum harmonization. The research and approval costs, including the time length of approval, will be reduced. However, this would suggest that the regulatory environment is not being fully harmonized in across EU member states. Under the condition that a Directive is chosen as a regulative instrument this will, however, also apply for measures of maximum harmonization as MSs enjoy freedom in how to apply the regulations regarding GMMs in their national legislation.

The hurdle rates derived from the model give an idea of the impact of the approval time length and other costs on the willingness of companies to invest in techniques that contain GMMs. As industries were not differentiated in this article, the cost and time length of approval may differ between industries and are not yet exactly known. Therefore, the results should be interpreted carefully. However, generally, the results show that the uncertainty companies face regarding the regulatory environment of GMMs in the EU has a strong effect on the postponement of investment in these new techniques. While deciding about investment in techniques that use GMMs, ex-post liability after the product has entered the market has only a small negative effect on the hurdle rate. This ex-post liability could therefore be used as a substitute for approval costs to strengthen the incentives of different industries to invest in GMM techniques, not only at the EU but also at the international level.

Our model suggests that it would be beneficial if there was regulatory harmonization at both the EU and international levels. This would result in an increase in investments in new techniques that use genetic modification. This is advantageous not only for sectors that use GMMs but also in different areas where these new techniques might be used. Despite the fact that these new techniques are emerging, an increase in investments is not expected in the short term. However, considering the challenges that humanity has to face in the future and the large-scale production in several industries, such as the dairy sector, it is expected that these new techniques will attract more and more attention.

Our model will be enriched as more details about the benefits that can be generated from the use of GMMs are revealed. These benefits could include international market access and competition. If more GMM-containing products have entered the market, these benefits should be taken into account in future research.

ORCID

Justus Wesseler https://orcid.org/0000-0002-6009-8543
Gijs Kleter https://orcid.org/0000-0001-7030-1149
Kai P. Purnhagen https://orcid.org/0000-0002-9902-7347

ENDNOTES

[1] As a delay allows to observe the level of benefits, and if the benefits are low it does not pay for investing in developing the GMM. The implicit assumption made is that B_l is always that low, that investment would not pay. As over time new information with respect to benefits arrive, waiting allows to avoid the losses in case benefits are low as illustrated in the seminal paper by Arrow and Fisher (1974). The problem addressed here has been formulated as a discrete-time, discrete-state model. One can immediately think of a continuous time, continuous state version. This substantially complicates the analysis and interpretation of results (Wesseler & Zhao, 2019) and does often not provide additional insights that are of importance for assessing real options (Balikcioglu et al., 2011), while for financial options this might be different.

[2] The problem could also be addressed via the implicit function theorem. This would complicate the math substantially, but as we expect provide similar results. We leave it for further research to investigate this proposition in more detail.

[3] Please note, the term $qe^{-ut}B_h$ has been dropped as we are mainly interested in the effects of R&D and approval costs.

REFERENCES

Aguilera, Jaime, Ana R. Gomes, and Irina Olaru. 2013. "Principles for the Risk Assessment of Genetically Modified Microorganisms and their Food Products in the European Union." *International Journal of Food Microbiology* 167(1): 2–7. https://doi.org/10.1016/j.ijfoodmicro.2013.03.013.

Arrow, Kenneth J., and Anthony C. Fisher. 1974. "Environmental Preservation, Uncertainty, and Irreversibility." *The Quarterly Journal of Economics* 88(2): 312. https://doi.org/10.2307/1883074.

Arrow, Kenneth J., Maureen L. Cropper, George C. Eads, Robert W. Hahn, Lester B. Lave, Roger G. Noll, and Paul R. Portney. 1996. "Is There a Role for Benefit-Cost Analysis in Environmental, Health, and Safety Regulation?" *Science* 272(5259): 221–2. https://doi.org/10.1126/science.272.5259.221.

Balikcioglu, Metin, Paul L. Fackler, and Robert S. Pindyck. 2011. "Solving Optimal Timing Problems in Environmental Economics." *Resource and Energy Economics* 33(3): 761–8. https://doi.org/10.1016/j.reseneeco.2010.12.004.

Bilal, Muhammad, and Hafiz M. N. Iqbal. 2019. "Sustainable Bioconversion of Food Waste into High-Value Products by Immobilized Enzymes to Meet Bio-Economy Challenges and Opportunities – A Review." *Food Research International* 123: 226–40. https://doi.org/10.1016/j.foodres.2019.04.066.

Bovay, John, and Julian M. Alston. 2018. "GMO Food Labels in the United States: Economic Implications of the New Law." *Food Policy* 78: 14–25.

Cao, Jiling, Edmond Sanganyado, Wenhua Liu, Wei Zhang, and Ying Liu. 2019. "Decolorization and Detoxification of Direct Blue 2B by Indigenous Bacterial Consortium." *Journal of Environmental Management* 242: 229–37.

Cox, David Roxbee, and David Oakes. 1984. *Analysis of Survival Data*. New York, NY: Chapman and Hall/CRC. https://www.taylorfrancis.com/books/mono/10.1201/9781315137438/analysis-survival-data-cox-oakes.

Deckers, Marie, Kevin Vanneste, Raf Winand, Marijke Hendrickx, Pierre Becker, Sigrid C. J. De Keersmaecker, Dieter Deforce, Fraiture Marie-Alice, and Nancy H. C. Roosens. 2020. "Screening Strategy Targeting the Presence of Food Enzyme-Producing Fungi in Food Enzyme Preparations." *Food Control* 117: 107295. https://doi.org/10.1016/j.foodcont.2020.107295.

Denby, Charles M., Rachel A. Li, Van T. Vu, Zak Costello, Weiyin Lin, Leanne Jade Chan, Joseph Williams, et al. 2018. "Industrial Brewing Yeast Engineered for the Production of Primary Flavor Determinants in Hopped Beer." *Nature Communications* 9(1): 1–10.

Drury, Georgina, Siobhan Jolliffe, and Tarit K. Mukhopadhyay. 2019. "Process Mapping of Vaccines: Understanding the Limitations in Current Response to Emerging Epidemic Threats." *Vaccine* 37(17): 2415–21.

EFSA. 2011. "Guidance on the Risk Assessment of Genetically Modified Microorganisms and their Products Intended for Food and Feed Use." *EFSA Journal* 9(6): 2193.

EUR-Lex. 2018. "Judgment of the Court in Case C-528/16." https://curia.europa.eu/juris/document/document.jsf;jsessionid=A4E7148EFB69470728D12255A3999D05?text=&docid=204387&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=1161518.

European Commission. 2003. "Regulation (EC) No 1830/2003 of the European Parliament and of the Council of 22 September 2003 Concerning the Traceability and Labelling Of Genetically Modified Organisms and the Traceability Of Food and Feed of Produced From Genetically Modified Organisms and Amending Directive 2001/18/EC." *Official Journal of the European Union L* 268: 24–8. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32003R1830.

European Commission. 2004. "Standing Committee on the Food Chain and Animal Health, Section on Genetically Modified Food and Feed and Environmental Risk, Summary Record of the 3rd Meeting – 24 September 2004." European Commission, Brussels, Belgium. https://amfep.org/_library/_files/standing-committee-on-the-food-chain-and-animal-health-sector-confirms-that-foods-and-feeds-produced-by-fermentation-with-gmms-genetically-modified-microorganisms-used-in-containment-a.pdf.

European Commission. 2019. "Standing Committee on Plants, Animals, Food and Feed Section Genetically Modified Food and Feed, 30 April 2019: Summary Report [sante.ddg2.g.5(2019)3732288]." European Commission, Brussels, Belgium.

European Commission. 2021. "Study on the Status of New Genomic Techniques under Union Law and in Light of the Court of Justice Ruling in Case C-528/16 ()." https://ec.europa.eu/food/system/files/2021-04/gmo_mod-bio_ngt_eu-study.pdf.

European Parliamentary Research Service. 2017. "The EU's General Food Law Regulation: An Introduction to the Founding Principles and the Fitness Check." https://www.europarl.europa.eu/thinktank/en/document.html?reference=EPRS_IDA(2017)595906.

Frederiks, Coen, and Justus Wesseler. 2019. "A Comparison of the EU and US Regulatory Frameworks for the Active Substance Registration of Microbial Biological Control Agents." *Pest Management Science* 75(1): 87–103.

Glandorf, Debora C. 2019. "Re-Evaluation of Biosafety Questions on Genetically Modified Biocontrol Bacteria." *European Journal of Plant Pathology* 153(1): 243–51.

Gomez, Fernando, and Juan Jose Ganuza. 2011. "How to Build European Private Law: An Economic Analysis of the Lawmaking and Harmonization Dimensions in European Private Law." *European Journal of Law and Economics* 33(3): 481–503.

Gosal, S. K., Jaspreet Kaur, and Jupinder Kaur. 2020. "Microbial Biotechnology: A Key to Sustainable Agriculture." In *Phyto-Microbiome in Stress Regulation*, edited by Manoj Kumar, Vivek Kumar, and Ram Prasad, 219–43. Singapore: Springer.

Gupta, Saurabh, and Daljeet Singh. 2017. "Role of Genetically Modified Microorganisms in Heavy Metal Bioremediation." In *Advances in Environmental Biotechnology*, edited by Raman Kumar, Anil Kumar, Sharma Sarabjeet, and Sarabjeet Singh Ahluwalia, 197–214. Singapore: Springer.

Jin, Yan, Dusan Drabik, Nico Heerink, and Justus Wesseler. 2019. "Getting an Imported GM Crop Approved in China." *Trends in Biotechnology* 37(6): 566–9. https://doi.org/10.1016/j.tibtech.2019.02.004.

Kalaitzandonakes, Nicholas, Julian Alston, and Kent Bradford. 2007. "Compliance Costs for Regulatory Approval of New Biotech Crops." *Nature Biotechnology* 25(4): 509–11.

Kauffmann, Florence, Pierre Van Damme, Geert Leroux-Roels, Corinne Vandermeulen, Nele Berthels, Claire Beuneu, and Stéphanie Mali. 2019. "Clinical Trials with GMO-Containing Vaccines in Europe: Status and Regulatory Framework." *Vaccine* 37(42): 6144–53.

Kishor, Roop, Diane Purchase, Ganesh Dattatraya Saratale, Rijuta Ganesh Saratale, Luiz Fernando Romanholo Ferreira, Muhammad Bilal, Ram Chandra, and Ram Naresh Bharagava. 2021. "Ecotoxicological and Health Concerns of Persistent Coloring Pollutants of Textile Industry Wastewater and Treatment Approaches for Environmental Safety." *Journal of Environmental Chemical Engineering* 9(2): 105012. https://doi.org/10.1016/j.jece.2020.105012.

Kolstad, Charles D., Thomas S. Ulen, and Gary V. Johnson. 1990. "Ex Post Liability for Harm vs. Ex Ante Safety Regulation: Substitutes or Complements?" *The American Economic Review* 80(4): 888–901.

Kumar, Sandeep, Vikas Kumar Dagar, Yogender Pal Khasa, and Ramesh Chander Kuhad. 2013. "Genetically Modified Microorganisms (GMOs) for Bioremediation." In *Biotechnology for Environmental Management and Resource Recovery*, edited by Ramesh Chander Kuhad and Ajay Singh, 191–218. New York, NY: Springer.

Kumar, Amit, Gaurav Sharma, Mu. Naushad, Ala'a H. Al-Muhtaseb, Alberto García-Peñas, Genene Tessema Mola, Chuanling Si, and Florian J. Stadler. 2020. "Bio-Inspired and Biomaterials-Based Hybrid Photocatalysts for Environmental Detoxification: A Review." *Chemical Engineering Journal* 382: 122937.

Letti, Luiz A., Junior, Francisco M. Destéfanis Vítola, Gilberto Vinícius de Melo Pereira, Susan G. Karp, Adriane B. Pedroni Medeiros, Eduardo S. Ferreira da Costa, Lucas Bissoqui, and Carlos R. Soccol. 2018. "Solid-State Fermentation for the Production of Mushrooms." In *Current Developments in Biotechnology and Bioengineering*, edited by Ashok Pandey, Christian Larroche, and Carlos Ricardo Soccol, 285–318. Amsterdam, NL: Elsevier.

Leunda, Amaya, and Katia Pauwels. 2019. "GMO Regulatory Aspects of Novel Investigational Vaccine Candidates." In *Vaccines*, edited by Vijay Kumar. London, UK: IntechOpen. https://doi.org/10.5772/intechopen.85341.

Liu, Xiangyang, and Chandrakant Kokare. 2017. "Microbial Enzymes of Use in Industry." In *Biotechnology of Microbial Enzymes*, edited by Goutam Brahmachari, 267–98. London, UK: Academic Press.

Mallikarjuna, Nimgampalle, and Kuna Yellamma. 2019. "Genetic and Metabolic Engineering of Microorganisms for the Production of Various Food Products." In *Recent Developments in Applied Microbiology and Biochemistry*, edited by Viswanath Buddolla, 167–82. London, UK: Academic Press.

Mathur, Rita. 2018. "Genetic Engineering and Biosafety in the Use of Genetically Modified Foods." *International Journal of Advanced Scientific Research and Management* 2018(I): 76–82.

Mertens, Stijn, Brigida Gallone, Jan Steensels, Beatriz Herrera-Malaver, Jeroen Cortebeek, Robbe Nolmans, Veerle Saels, Valmik K. Vyas, and Kevin J. Verstrepen. 2019. "Reducing Phenolic Off-Flavors through CRISPR-Based Gene Editing of the FDC1 Gene in *Saccharomyces cerevisiae* x *Saccharomyces eubayanus* Hybrid Lager Beer Yeasts." *PLoS One* 14(1): e0209124.

National Academy of Sciences Leopoldina, Union of German Academies of Sciences and the German Research Foundation 2019. "Towards a Scientifically Justified, Differentiated Regulation of Genome Edited Plants in the EU." Halle, Germany.

OECD. 2011. *Industrial Biotechnology and Climate Change*. Paris: OECD.

Parisi, Claudia, and Emilio Rodriguez-Cerezo. 2021. *Current and Future Market Applications of New Genomic Techniques*. Luxembourg: Publications Office of the European Union.

Pinsky, Mark A., and Samuel Karlin. 2011. *An Introduction to Stochastic Modeling*. London: Academic Press.

Purnhagen, Kai P. 2014. "The Virtue of Cassis de Dijon 25 Years Later—It Is Not Dead, It Just Smells Funny." In *Varieties of European Economic Law and Regulation*, edited by Kai Purnhagen and Peter Rott, 315–42. New York, NY: Springer.

Purnhagen, Kai P., and Justus Wesseler. 2019. "Maximum Vs Minimum Harmonization: What to Expect from the Institutional and Legal Battles in the EU on Gene Editing Technologies." *Pest Management Science* 75 (9): 2310–5.

Purnhagen, Kai P., Stephan Clemens, Dennis Eriksson, Louise O. Fresco, Jale Tosun, Matin Qaim, Richard G. F. Visser, Andreas P. M. Weber, Justus H. H. Wesseler, and David Zilberman. 2021. "Europe's Farm to Fork Strategy and Its Commitment to Biotechnology and Organic Farming: Conflicting or Complementary Goals?" *Trends in Plant Science* 26(6): 600–6. https://doi.org/10.1016/j.tplants.2021.03.012.

Raveendran, Sindhu, Binod Parameswaran, Sabeela Beevi Ummalyma, Amith Abraham, Anil Kuruvilla Mathew, Aravind Madhavan, Sharrel Rebello, and Ashok Pandey. 2018. "Applications of Microbial Enzymes in Food Industry." *Food Technology and Biotechnology* 56(1): 16–30.

Scheepmaker, Jacqueline W. A., Petra A. M. Hogervorst, and Debora C. M. Glandorf 2016. "Future Introductions of Genetically Modified Microbial Biocontrol Agents in the EU: Are Current EU Legislation and Risk Assessment Fit for Purpose?" *RIVM Letter Report 2016-0057*.

Shavell, Steven. 1984. "A Model of the Optimal Use of Liability and Safety Regulation." *RAND Journal of Economics* 15(2): 271–80. https://doi.org/10.2307/2555680.

Shleifer, Andrei. 2010. "Efficient Regulation." In *Regulation Versus Litigation: Perspectives from Economics and Law*, edited by Daniel P. Kessler, 27–44. Chicago, IL: University of Chicago Press. https://doi.org/10.7208/9780226432212-004.

Smart, Richard, Matthias Blum, and Justus Wesseler. 2015. "EU Member states' Voting for Authorizing Genetically Engineered Crops: A Regulatory Gridlock." *German Journal of Agricultural Economics* 64: 244–62. https://ageconsearch.umn.edu/record/270183/

Smart, Richard D., Matthias Blum, and Justus Wesseler. 2017. "Trends in Approval Times for Genetically Engineered Crops in the United States and the European Union." *Journal of Agricultural Economics* 68(1): 182–98. https://doi.org/10.1111/1477-9552.12171.

Soreanu, Inga, Adi Hendler, Danielle Dahan, Daniel Dovrat, and Amir Aharoni. 2018. "Marker-Free Genetic Manipulations in Yeast Using CRISPR/CAS9 System." *Current Genetics* 64(5): 1129–39.

Tramper, Johannes, and Yang Zhu. 2011. *Modern Biotechnology*. Wageningen, NL: Wageningen Academic Publishers.

Waltz, Emily. 2016. "Gene-Edited CRISPR Mushroom Escapes US Regulation." *Nature* 532(7599): 293–3.

Wesseler, Justus. 2014. "Biotechnologies and Agrifood Strategies: Opportunities, Threats and Economic Implications." *Bio-based and Applied Economics* 3(3): 187–204.

Wesseler, Justus, and Kai Purnhagen. 2020. "Is the Covid-19 Pandemic a Game Changer in GMO Regulation?" *EuroChoices* 19(3): 49–52. https://doi.org/10.1111/1746-692x.12301.

Wesseler, Justus, and Jinhua Zhao. 2019. "Real Options and Environmental Policies: The Good, the Bad, and the Ugly." *Annual Review of Resource Economics* 11(1): 43–58. https://doi.org/10.1146/annurev-resource-100518-094140.

Wozniak, Chris A., Gwendolyn McClung, Joel Gagliardi, Mark Segal, and Keith Matthews. 2012. "Regulation of Genetically Engineered Microorganisms under FIFRA, FFDCA and TSCA." In *Regulation of Agricultural Biotechnology: The United States and Canada 57–94*. Dordrecht: Springer.

Zaheer, Mohad R., and Anamika Gupta. 2019. "Current Development and Future Perspectives of Microbial Enzymes in the Dairy Industry." In *Enzymes in Food Biotechnology*, edited by Mohammed Kuddus, 287–302. London, UK: Academic Press. https://www.sciencedirect.com/science/article/pii/B9780128132807000177.

Zhang, Yi, Timothy Geary, and Benjamin K. Simpson. 2019. "Genetically Modified Food Enzymes: A Review." *Current Opinion in Food Science* 25: 14–8. https://doi.org/10.1016/j.cofs.2019.01.002.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Wesseler, Justus, Gijs Kleter, Marthe Meulenbroek, and Kai P. Purnhagen. 2022. "EU regulation of genetically modified microorganisms in light of new policy developments: Possible implications for EU bioeconomy investments." *Applied Economic Perspectives and Policy* 1–21. https://doi.org/10.1002/aepp.13259