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Uncertainty, institutions and regulatory responses to emerging technologies: CRISPR Gene editing in the US and the EU (2012–2019)

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Abstract

This study aims to improve theoretical accounts of regulatory responses to emerging technologies by proposing a model of regulatory development, which incorporates a role for types of uncertainty and for existing regulatory institutions. Differently from existing theories of regulatory development, the model proposed here posits a sequence of cyclical activities where regulatory responses arise in incremental fashion out of efforts to make sense of emerging technologies and to ponder the applicability of existing regulatory tools. The model is discussed on the basis of the comparison between regulatory responses to the emergence of CRISPR gene editing in the US and the EU in the period 2012–2019. The comparison between the two cases suggests how regulatory responses to emerging technologies are affected by expectations of future technological and regulatory developments and by existing regulatory institutions.

Keywords: CRISPR, emerging technology, regulatory institution, uncertainty.

1. Introduction

The increased pace of scientific discoveries and technological advances of the last decades poses novel challenges for regulators. Emerging technologies - here defined as new technologies characterized by radical novelty, relatively fast growth, coherence, prominent impact, and uncertainty (Rotolo *et al.* 2015) –pose new sort of dangers and hazards to individuals and to the natural environment, build on mechanisms whose underlying cause-effect relationships are not fully understood, and lend themselves – as "technological platforms" – to a plethora of possible uses (Levi-Faur & Comaneshter 2007; Brownsword 2008; Hodge *et al.* 2009; Marchant *et al.* 2009; Roca *et al.* 2017; Tzur 2017). When confronted with emerging technologies, policy-makers and regulators lack knowledge about what precisely the emerging technology entails, how unwelcome effects of the emerging technology can be tackled, and which sorts of applications of the emerging technologies they should be specifically concerned with (Mandel 2009). Similar issues are confronted across a variety of technological advances in such diverse areas as, for example from cryptoassets (Whitford & Anderson 2020) to nanomaterials and from autonomous systems (Firlej & Taeihagh 2020) to the Internet-of-Things (Brass & Sowell 2020).

Existing theories of regulatory development provide some explanations for the formation of new regulatory regimes. As the introduction to this Special Issue remarked (Howlett *et al.* 2020), the life-cycle theory of regulation (Bernstein 1955; Howlett & Newman 2013) holds that regulatory institutions arise and consolidate through a sequence of stages, which span from the acknowledgment of a public problem and the organization of advocacy groups that call for a solution to the capture of regulators by the regulated industry. Yet, theories of regulatory

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development pay little attention to the role of uncertainty (Kaebnick *et al.* 2016; Roca *et al.* 2017) about the nature of new technologies, the effects of technological development, and the consequences of regulatory responses. Theories of regulatory development also seem to downplay the role of existing regulatory institutions, which should be rather taken more into account because they provide important resources for understanding emerging technologies and for orienting trajectories of technology development.

This study aims to improve theoretical accounts of regulatory responses to emerging technologies. Building on Lindblom's (1959, 1968) arguments about disjointed problem solving and incrementalism (Atkinson 2011) and Milliken's (1987) analysis of types of uncertainty (namely, state uncertainty, effect uncertainty, and response uncertainty – three categories that help disentangle the multidimensional feature of the uncertainty construct; McKelvie *et al.* 2011), this study investigates how regulatory responses to emerging technologies develop in a gradual and iterative fashion. We propose a model that consists of a sequence of cyclical activities where regulatory responses arise in incremental fashion out of efforts to make sense of emerging technologies and to ponder the applicability of existing regulatory tools. The activities – namely, developing the emerging technology, launching emerging technology applications, applying (existing or adjusted) regulations, apprising the emerging technology impact, and adjusting regulations–exert mutual influences through consequential and anticipatory linkages. The model is intended to help explain the process dynamics and the content of regulatory responses to emerging technologies during the search for agreed regulatory standards and enforcement measures.

The empirical part of this study consists of a comparative analysis of the early regulatory responses to CRISPR gene-editing technology in the US and the EU. Developed as a technique for genetic editing since 2012, CRISPR (which is the acronym of Clustered Regularly Interspaced Short Palindromic Repeats and a shorthand for CRISPR-cas9, which means CRISPR-associated RNA-guided endonuclease cas9) provides an exemplar case of emerging technology. CRISPR is widely regarded as having potentially disruptive impacts on diverse areas – like, for example from plant breeding to cancer diagnosis and treatment – and controversial effects – like, for example from bringing about the extinction of selected species to enhancing desired human features (Patsali *et al.* 2019). The comparison between regulatory responses to CRISPR in the US and the EU helps draw analytical arguments about how types of uncertainty and existing regulatory institutions affect regulatory responses to emerging technologies.

The rest of the study is organized as follows. The next section will discuss a theoretical framework for explaining regulatory responses to emerging technologies. The following three sections will narrate the rise of CRISPR and the early regulatory responses in the US and the EU in the period 2012–2019. The sixth section will discuss similarities and differences between the regulatory responses to CRISPR in the US and the EU and draw implications for the theorization of regulatory responses to emerging technologies. Finally, the last section will draw conclusions.

2. Uncertainty, institutions, and regulatory responses to emerging technologies

Emerging technologies trigger very diverse regulatory responses (Brownsword & Yeung 2008; Taeihagh & Lim 2019). At one extreme, policy-makers and regulators may prohibit the use of new technologies altogether; at another one, they may tolerate – or even encourage –any possible creative and rampant application of novel techniques. In between the extremes, policy-makers and regulators may follow moderate approaches to monitor and guide trajectories of technological development and the launch of their applications. Policy-makers and regulators may limit the manufacture, import, and commercialization of products obtained through techniques that bear undecided effects on health, safety, and the environment – like in the way the precautionary principle inspired the regulation of genetically modified organism (GMO) food and feed in the EU since the early 2000s that effectively resulted in the outlaw of GMOs (Sunstein 2005; Bourguignon 2015; Baum 2018). Alternatively, policy-makers and regulators may exert only as much oversight as it is strictly necessary to ensure safety, security, fairness, and justice in the development and use of emerging technologies – like in the way regulatory parsimony informed regulatory attitudes toward synthetic biology in the US since the early 2010s (Bedau *et al.* 2010; US PCSBI 2010; Gutmann 2011; Gutmann & Moreno 2018). Different regimes of risk governance arise depending on how risks that are posed by emerging technologies are socially constructed and reasoned about (Renn 2017).

Existing theories of regulation seem poorly equipped to explain regulatory responses to emerging technologies. Private interest theories of the regulation (Peltzman 1976;Posner 1974;Stigler 1971) are primarily concerned with issues that arise from information asymmetry (Baldwin *et al.* 2012) and, relatedly, regulatory capture (Laffont & Tirole 1991). The context of emerging technologies, instead, is characterized by widespread uncertainty concerning the prospective use of the technology in addition to information asymmetry between actors. Public interest theories of the regulation (Chang 1997;Christensen 2011), on the other hand, are concerned with the maximization of social welfare, but, in the context of emerging technologies, uncertainty prevents the regulators from anticipating future uses of the technology and from selecting the most advantageous forms of regulatory intervention. In addition, emerging technologies typically open up opportunities for new entrants to challenge industry incumbents or for first movers to disrupt existing industrial regimes (Danneels 2004, 2006). In such a scenario, conventional regulatory concerns toward restraining the market power of monopolies or oligopolies are relatively immaterial, while regulator's attention rather focuses on reviewing the entry into the market of a stream of innovative products in high-velocity environments (Wirz *et al.* 2007). Theories of regulatory development provide a limited account of the regulation of emerging technologies, too. The life-cycle theory of regulation, in particular, provides a sequence of stages through which regulatory institutions and practices develop (Bernstein 1955). While progressing through the stages of gestation, youth, maturity, and old age, regulatory regimes would shift their focus from the very early formulation of regulatory problems to the struggle for the preservation of the status quo once the industry has fully captured the regulators. Subsequent improvements to the original model inserted further intermediary stages – namely, infancy and childhood (Howlett & Newman 2013)– that provided a more detailed account of early regulatory activities, such as, for example efforts to adapt existing statutes and rules to current problems and to launch research programs for hazard characterization and risk assessment.

Existing theories of regulatory development do not pay enough attention to the role of uncertainty that arises from emerging technologies, which is important because uncertainty affects how individuals make sense of regulatory problems and devise regulatory responses (Kaebnick *et al.* 2016; Roca *et al.* 2017). In addition, existing theories of regulatory development do not grant enough consideration to the role of existing regulatory institutions, which are pivotal because emerging technologies do not typically arise in a "regulatory void" but originate from the periphery of existing technological domains, whose regulations provide antecedents to understand emerging technologies (Weber & Glynn 2006) and resources to orient technology trajectories (Dolata 2009).

Lindblom's works (Lindblom 1959, 1968) provide a conceptual underpinning for theorizing about the role of uncertainty and of existing regulatory institutions in regulatory development. Contrary to a view of policy-making as a rational and linear process (Hofer and Schendel 1978; Otway & Ravetz 1984), policy decisions are posited to take place under conditions of incomplete information about alternatives, costs and benefits, of limited calculative capacity, and of disagreements about values (Braybrooke & Lindblom 1963). Policy-makers cope with these conditions by making successive limited comparisons between options available, which often result in small adjustments with respect to the status quo (Atkinson 2011). Decisions are eventually made when policies, aims, and values are selected in concert under favorable circumstances that arise from the successful coupling of somebody's preferred solution with a shared formulation of a problem (Cohen *et al.* 1972;March 1978; Olsen 2001).

Lindblom's works (Lindblom 1959, 1968) are relatively silent about sources of uncertainty and how they affect the policy-making process. A contribution is offered, in this respect, by the work of Milliken (1987), who distinguished between state uncertainty, effect uncertainty, and response uncertainty. State uncertainty (or perceived environmental uncertainty) refers to an individual's inability to predict changes in the technological environment (or part of it). Effect uncertainty relates to an individual's inability to predict the effects of changes in the technological environment on a particular organization (Lawrence & Lorsch 1967; Duncan 1972). Response uncertainty pertains to an individual's inability to see what response options to changes in the technological environment are available and appraise their consequences (Conrath 1967; Taylor 1984). Taken together with Lindblom's (1959, 1968) arguments about disjointed problem solving and incrementalism, Milliken's (1987) classification provides a framework to analyze the role of different types of uncertainty in the regulatory development process.

Table 1 identifies issues that the three types of uncertainty pose with respect to three component parts of the pre-decisional stage of the regulatory development process, namely the definition of the regulatory problem, the

Table 1 Issues that source of uncertainty pose in the component parts of the pre-decisional stage of the regulatory development process for emerging technologies

Component parts of the pre-decisional stage	Types of uncertainties		
	State uncertainty	Effect uncertainty	Response uncertainty
Definition of policy problems	What opportunities and threats are posed by the emerging technology?	How does the emerging technology affect the role and performance of the regulators?	How does a regulatory response affect the impact of the emerging technology?
Scan of the alternatives	What can be done about the emerging technology?	What can the regulators do to cope with the impact of the emerging technology on their role and performance?	What can the regulators do to affect the impact of the emerging technology?
Appraisal of the options available	What is the most advantageous way to cope with the emerging technology?	Which is the most advantageous action for the regulators to cope with the emerging technology?	What is the most advantageous action for the regulators to affect the impact of emerging technology?

search for alternative regulatory responses, and the appraisal of the regulatory options available (Bendor 1995; Dryzek 1983; Jones & Baumgartner 2005). In the context of emerging technologies, state uncertainty relates to the inability to predict future scientific discoveries and the launch of applications of the new technology; effect uncertainty refers to the inability to predict the impact of the emerging technology on particular stakeholders' organizations; and response uncertainty arizes from the inability to predict, which regulatory tools are more suitable to the specific features of the emerging technology. These uncertainties obfuscate the pre-decisional stage of the regulatory development process. The definition of the regulatory problem is affected by issues of an epistemic sort (Levidow 2001) because of uncertainties about the nature and the effects of the emerging technology. The search for alternative regulatory responses is dependent on issues of applicability of existing regulatory institutions and tools to the uses of the emerging technology (Yalnazov 2018). The appraisal of the regulatory options available is conditional on the strategic behavior of the regulated firms (Allaire & Firsirotu 1989; van Huyck *et al.* 1990), who adjust their conduct – for example whether to invest in the emerging technology – depending on the regulatory response (Rogge *et al.* 2011; Lopez *et al.* 2017). The strategic behavior of the regulated firms also provides a source of information asymmetry with policy-makers and regulators, which results in further uncertainty about the future trajectory of technological development and its effects.

The above discussion suggests that uncertainties make the process of regulatory development in the context of emerging technologies relatively under-determined and open-ended. We propose, instead, that the regulatory development process follows a pattern (Howlett *et al.* 2020). In the model described below, the regulatory response to emerging technologies consists of a sequence of cyclical activities, namely developing the emerging technology, launching emerging technology applications, applying (existing or adjusted) regulations, apprising the emerging technology impact, and adjusting regulations. The sequence of activities is repeated over time so that regulatory adjustment at the end of a cycle is followed by further development of the emerging technology at the beginning of the following cycle. Figure 1 provides a pictorial representation of the model, where reiterations of the sequence of activities unfold along the time dimension (i.e. graphically, the cycle is unfolded as a helix). The model illustrated in Figure 1 also posits that the activities of regulatory development are connected by consequential and anticipatory linkages. Consequential linkages consist of triggers between an activity and a following one, while anticipatory linkages consist of stimuli that arise from expectations about future – albeit uncertain – effects of activities onto subsequent ones.

Uncertainty plays an important role in the model. Consequential linkages entail that activities create conditions that affect, in part, the performance of subsequent activities. Anticipatory linkages, instead, imply that activities are carried out, in part, depending on expectations about the future development of the emerging technology, of its applications, and of regulatory responses. The three types of uncertainties (Milliken 1987)

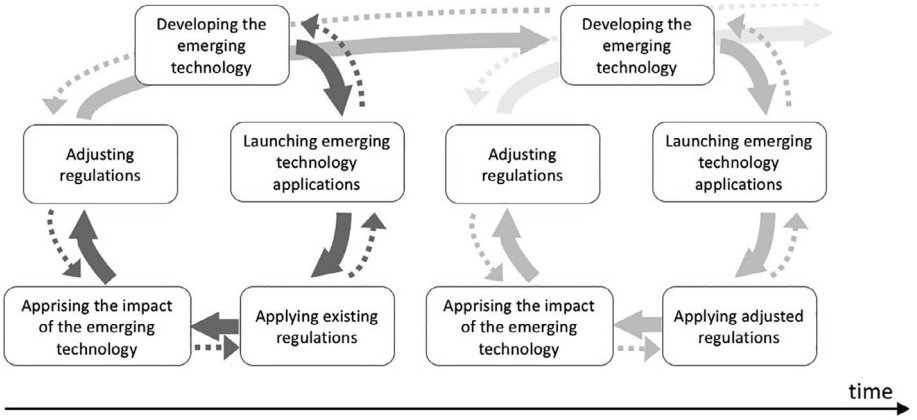

Figure 1 A model of development of regulatory responses to emerging technologies with consequential linkages (solid bold arrows) and anticipatory linkages (dotted thin arrows).

prevent individuals from anticipating future technological and regulatory developments accurately, however. In addition, different individuals may perceive uncertainty differently and hold; therefore, different expectations, with the effect of hampering coordination and agreement between them. The presence of uncertainty and of anticipatory linkages makes the development of regulatory responses to emerging technologies highly dependent on contingent conditions of perceived uncertainty and expectations of individuals.

In addition, the model grants an important role in existing regulatory institutions, which are developed for regulating technological domains before the rise of emerging technologies. Existing regulatory institutions provide a source of default response to applications of emerging technologies by subjecting them to existing regulatory standards and mechanisms. The appraisal of the impact of emerging technologies, however, may trigger an adjustment of the installed regulatory system. Subsequent appraisals of the impact of the emerging technologies may result in a flow of successive regulatory adjustments until a stable regulatory regime is established, once technological and industrial developments become less turbulent. It is also possible, however, that the trajectory of successive regulatory adjustments is interrupted by the making of a regulatory reform, where novel regulatory institutions would radically supplant existing ones.

Existing regulatory institutions provide an important component part of the risk governance of emerging technologies, which consists of the procedures and criteria for tackling policy issues, granting stakeholder participation, resolving conflicts, and making decisions while managing resources and interests (Renn & Roco 2006). Risk governance informs how stakeholders and decision-makers understand the opportunities and challenges posed by emerging technologies and appraise possible courses of action. Risk governance systems may change over time, however. Reflection and debate upon the appropriateness of existing regulatory institutions, especially when coupled with perceived uncertainty and expectations of individuals, could result in regulatory adjustments when risk governance possesses adaptive and integrative capacity (Klinke & Renn 2012).

The rest of this study investigates the regulatory responses to emerging technologies through the comparative analysis of the rise of CRISPR gene editing in the US and the EU. With respect to other emerging technologies, CRISPR provides an exemplar instance of the regulatory development scenario under consideration, where uncertainty affects expectations about the future development of the CRISPR technology, of its applications, and of the regulatory response, and where regulations already exist for other techniques of genetic modification. In this sense, the case of CRISPR can be understood as a "critical case study" (Flyvbjerg 2006; Elman *et al.* 2016). The cases of CRISPR in the US and the EU, moreover, provide the opportunity to compare regulatory responses to emerging technologies in two regulatory regimes that have been often characterized as contrasting ones (Vogel 2012) – namely, the relative permissiveness in the US versus. the relative cautiousness in the EU toward possible sources of danger and hazard.

The narration of the regulatory responses to the rise of CRISPR begins in 2012 when the technique was discovered and terminates at the time of writing in 2019. Evidence was collected from the US Congress' "gov info"

of the US Government Publishing Office (congressional hearings, records, and reports) and EU Parliament's Public Register of Documents (questions to and answers from the EU Commission, in-depth analyzes, and studies), and from referenced academic and media sources. In the discussion part, evidence from the CRISPR case in the US and the EU is used to develop a theorization – in the form of explanatory hypotheses by abduction (Schurz 2008) –of regulatory responses to emerging technologies that aim to improve existing accounts of the regulatory development process.

3. The rise of CRISPR gene editing

Since the early 2010s, the interrelated fields of molecular biology, synthetic biology, and genetics were shaken by the rise of an emerging technology that promised to revolutionize such diverse areas as health, agriculture, and environmental preservation. Generally known as CRISPR, the technology opened up the possibility to accurately manipulate the DNA of living organisms in a cheaper and easier way than alternative approaches (Doudna & Charpentier 2014; Doudna & Sternberg 2017). Since its discovery, CRISPR sparked countless research projects and commercial enterprises across both industrialized countries and emerging economies. As the applications promised by CRISPR started to materialize, the issue of how the emerging technology should be regulated gained attention within scientific, industrial, and policy circles.

The discovery of CRISPR built on research that originated from the observation, made by Japanese researchers at Osaka University in 1987 (Ishino *et al*. 1987; Ishino *et al*. 2018), that a set of 29 nucleotides were repeated in the iap gene of *Escherichia coli*. In 1993, a research team led by Francisco Mojica at the University of Alicante explained the presence of repeated sequences of genetic code in *Haloferax mediterranei* as a defense reaction to virus attacks. The role of CRISPR – as the repeated gene structure had started to be called since 2002 – in the bacterial immune system and of cas9 in inactivating the virus attack was then investigated, in 2007, at the Danish food research firm Danisco (acquired by DuPont in 2011). In 2012, then, two research teams led, respectively, by Emmanuelle Charpentier (at Umeå University in Sweden) and Jennifer Doudna (at University of California, Berkeley) and by Feng Zhang and George Church (at Broad Institute) independently discovered that CRISPR and cas9 could be combined to perform accurate interventions into the genome (Lander 2016).

CRISPR technology consists of a process where the endonuclease enzyme cas9 cuts a DNA molecule at a specific location, where an altered gene is inserted with the guidance of small strands of RNA (Ledford 2015). The approach enables us to accurately remove selected genetic sequences and to replace them with beneficial or neutral genetic material. Differently from other forms of interventions, like, for example transcription activator-like effector nucleases (TALEN) and zinc-finger nucleases (ZFNs), CRISPR can take place within the same living organism (in vivo) rather than by manipulating DNA that is taken out of an organism (in vitro). In addition, CRISPR enables researchers to insert particular genetic materials at the desired location, rather than inducing random genetic changes through mutagenic chemicals or ionizing radiations. Furthermore, CRISPR does not require the transgenic combination of DNA traits from different organisms.

After its discovery in 2012, scientific and commercial interests toward CRISPR technology boomed. During the following years, research was done in such diverse areas as, for example editing the genome of mushrooms to prevent browning (at Pennsylvania State University in 2016) and correcting a genetic mutation linked to heart failure in human embryos (at the Oregon Health and Science University in 2017). A number of business ventures were launched to apply CRISPR to various areas. In 2013, for example Emmanuelle Charpentier co-founded CRISPR Therapeutics, which partnered with Vertex Pharmaceuticals to undertake, in 2018, the first CRISPR-based clinical trials for the treatment of beta-thalassemia and sickle cell disease. Another CRISPR pioneer, Jennifer Doudna, co-founded biotech companies Caribou Biosciences in 2011, Editas Medicine (with Feng Zhang) in 2013, and Intellia Therapeutics in 2014, and joined the advisory board of Synthego, a biotech company that provides researchers with bespoke engineered cells, in 2018. Another CRISPR pioneer, George Church, co-founded a biotech company in 2015 – eGenesis – that aimed to modify the pig genome to enable the transplantation of organs into humans without rejection. While many other biotech start-ups were founded, also large pharmaceutical companies like Bayer, Novartis, and Astrazeneca started undertaking CRISPR research projects.

The prospect of CRISPR applications triggered initiatives to share and coordinate scientific and technological advancements at the international level. Two International Summits on Gene Editing, held in Washington in

2015 and in Hong Kong in 2018, provided the main venue for scientists to reflect upon the potentials and implications of CRISPR, including its threatening and unwelcome effects on health, safety, and the environment. The announcement, made during the 2018 conference, by Chinese researcher He Jiankui that CRISPR gene editing had been successfully performed on two twin girls in order to make them resistant to infection from HIV/AIDS provoked harsh reactions toward the unrestrained use of CRISPR (Greely 2019). The scientific community strongly condemned the operation, which dramatically exposed that current regulatory systems did not prevent "maverick" scientists from carrying out ethically questionable initiatives (Cyranoski 2018; Kuersten & Wexler 2019). The Summits recommended that further CRISPR research should be subjected to stringent oversight while taking into account risks of inaccurate editing, effects on populations, possible interactions of the edited organism with the environment, implications on future generations, risk of spreading of the edited features across country borders, issues of increased social inequalities or possibility that gene editing is used coercively, and general moral and ethical considerations on altering human evolution (National Academies of Sciences, Engineering, and Medicine 2019).

4. Regulatory responses to CRISPR in the US (2012–2019)

In the US, the rise of CRISPR took place within a regulatory regime that had been designed around former genetic engineering techniques. In 1986, the White House Office of Science and Technology Policy issued the Coordinated Framework for the Regulation of Biotechnology, which provided that three federal agencies – namely, the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the Animal and Plant Health Inspection Service of the US Department of Agriculture (USDA-APHIS) – would share the task to review the introduction of products of modern biotechnology into the US market. The three federal agencies reacted to CRISPR products in different ways. USDA-APHIS (and EPA for modified plants with pesticide properties) would subject CRISPR products to existing regulation if they make use of genes of other organisms, while they would not apply them when a gene would be simply inactivated (USDA 2016). FDA, instead, subjected CRISPR products to regulatory review, as if even a tiny piece of new genetic material would make the product a "new drug" (Grant 2016). Applications of CRISPR in the sensitive area of human embryos, instead, were obstructed by a 1996 legislative rider (renewed by the Congress every year since) that had banned the use of federal funds for the creation of human embryos for research purposes or in research where human embryos would be destroyed (Tomlinson 2018). In 2016, an additional rider prohibited FDA to even acknowledge applications for an exemption to carry out research where a human embryo is intentionally created or modified to include a heritable genetic modification.

Limitations of the existing regulatory system to cope with CRISPR applications became increasingly apparent. Part of the scientific community and the industry lamented that existing regulations provided too many restrictions to the use of novel gene-editing approaches. On the other hand, more cautious arguments held that existing regulations were inadequate to tackle the risks posed by the unprecedented perils that originated from CRISPR. Further sources of concern arose within the national security system concerning the possibility that CRISPR could be used to engineer novel forms of bio-weapons, as indicated in the Worldwide Threat Assessment Reports by the Office of the Director of National Intelligence since 2016 (Clapper 2016).

Congress hearings help illustrate the concerns and attitudes toward CRISPR within US policy circles. Optimistic views toward CRISPR were provided, among others, by Dr. Martin Dickman (Distinguished Professor and Director of the Institute for Plant Genomics and Biotechnology of Texas A and M University) in a hearing before the Subcommittee on Research and Technology Committee on Science, Space and Technology of the House of Representatives in 2015 (Serial No. 114-54), when he argued that CRISPR would likely revolutionize breeding by creating variations in plants in a much faster way than before and that further funding should be provided to basic and risky research. This view was echoed by Dr. Stephen P. Moose (Denton and Elizabeth Alexander Professor of Maize Breeding and Genetics in the Department of Crop Sciences at the University of Illinois at Urbana-Champaign) in a hearing before the same Subcommittee in 2017 (Serial No. 115-35), when he explained that "we will be able to basically take a genome and it'll be like a word processor – edit, change a letter here or there – and do that in a designed way. So the speed and precision at which we'll be able to do that is wonderful." (p. 65).

In contrast, various Congress hearings convey a sense of threat, which could justify a more restrictive stance toward the use of CRISPR technology. In a hearing before the Committee on Homeland Security and Government Affairs of the US Senate in 2016, for example Senator Gary C. Peters expressed his concern toward new technologies such as CRISPR, which were available through fairly inexpensive kits and could be used in very nefarious ways (S. Hrg. 114-729). In 2017, Representative Daniel M. Donovan Jr. similarly warned that CRISPR could be used for manufacturing new biological weapons (hearing before the Subcommittee on Emergency Preparedness, Response and Communications of the Committee on Homeland Security of the House of Representatives, Serial No. 115-42). In 2018, Representative Dr. Ralph Lee Abraham also warned that well-funded groups that operate globally could use CRISPR to perpetrate evil actions with limited resources like a normal molecular biology lab (hearing before the Subcommittee on Emerging Threats and Capabilities of the Committee on Armed Services, H.A.S.C. No. 1115-63). Concerns with the threats posed by CRISPR and other new gene-editing techniques also started to affect the US state government. In July 2019, for example a first CRISPR law was passed in California (Senate Bill No. 180, Chapter 140) with the stated aim to protect users against the potential dangers and hazards of "biohacking" themselves.

The Federal Government undertook various actions to address the limitations of the existing regulatory system. After the White House Executive Office released a President Memorandum in 2015 (Executive Office of the US President 2015), the Biotechnology Working Group of the Emerging Technologies Interagency Policy Coordination Committee issued, in September 2016, the National Strategy for Modernizing the Regulatory System for Biotechnology Products (Executive Office of the US President 2016). The document outlined a vision and a set of principles for the update of the federal regulatory system to cope with the challenges posed by emerging technology, including gene editing. Following public consultations, in 2017 the White House Office of Science and Technology Policy (US OSTP 2017) issued the Update to the Coordinated Framework for the Regulation of Biotechnology, which clarified the allocation of roles and responsibilities for reviewing biotechnology products among USDA, FDA, and EPA. The Update to the Coordinated Framework concluded that the existing regulatory system was still sound with respect to protecting the health and the environment, although it also noted that inefficiency arose from uncertainty about agency jurisdiction and timeframes for reviews (Gallo *et al.* 2017).

The Update to the Coordinated Framework did not fully satisfy the scientific community, however. Criticisms addressed the failure of the Update to address distinctions between different kinds of genetic engineering and gene editing techniques and, relatedly, to clarify the regulatory environment for scientists, businesses, and investors (Lin 2017; Tomlinson 2018). In 2017, the National Academies of Sciences, Engineering and Medicine issued a report on "Preparing for Future Products of Biotechnology" (National Academies of Sciences, Engineering, and Medicine 2017), which called for strengthening scientific capabilities, tools, expertise, and horizon scanning of USDA, FDA, and EPA, making more use of pilot projects, and increasing government investment in biotechnology research. In 2018, the National Academies also published another report on "Human Genome Editing" (National Academies of Sciences, Engineering, and Medicine 2018), which contemplated the possibility to edit germline cells when filling unmet medical needs and provide benefit to the subjects whose genes are altered. The Federal Government cautiously responded to these calls for more flexibility toward products created with new technologies, for example by requiring – through an executive order of the US President in June 2019 – that government agencies identify relevant regulations and guidance documents that could be streamlined and help bringing innovative products to the market and exempt low-risk products of agricultural biotechnology from undue regulation (Executive Office of the US President 2019).

5. Regulatory responses to CRISPR in the EU (2012–2019)

In the EU, CRISPR arose within a context where regulation of genetic engineering techniques had been provided by EU Directive 2001/18 ("GMO directive"), which – following the precautionary principle – subjected R&D trials, environmental release and commercialization of GMOs to strict procedural requirements. The peculiar features of CRISPR, however, made it unclear whether the application of CRISPR technology should be subjected to existing regulations. Already in February 2014, the European Parliament adopted a resolution that called the Commission to clarify the regulatory status of new breeding techniques (EU Parliament 2014a), which was followed in March 2014 by another resolution that established a separate approval process for cisgenic and

transgenic plants (EU Parliament 2014b). The European Parliament also exhorted the Commission to support the new breeding techniques, which were expected to help boost productivity and growth of European agriculture, through the Horizon 2020 program.

The importance of CRISPR for the European agriculture sector was restated also in other initiatives by the European Parliament. In May 2016, for example the Committee on Agriculture and Rural Development issued the Report on Technological Solutions for Sustainable Agriculture in the EU, which acknowledged the potential offered by precision breeding for achieving crop improvement and tackling pressing issues, such as population growth, increased demand for healthy food and optimal nutrition, reduced land availability, environmental damage, water shortage, and the emergence of new pests and diseases. The report called the Commission to "improve its regulatory framework in line with the principles of Better Regulation to ensure timely, efficient and effective decision-making procedures" (EU Committee on Agriculture and Rural Development 2016, p. 73), also based on the new Scientific Advice Mechanism – a service created by European Commissioner Jean-Claude Junker in 2015 to provide advice to European Commissioners on science and technology matters.

Despite the perceived importance of CRISPR for European agriculture, the issue of regulation of the use of emerging technology remained unsettled. In 2015, the European Academies Science Advisory Council (EASAC 2015) suggested that the products of new breeding techniques like CRISPR should not fall under GMO legislation when they do not contain alien sequences of DNA. This view was shared among various entities also at the Member States level. In Germany, for example the Federal Office for Consumer Protection and Food Safety (BVL) stated that plants generated by CRISPR do not constitute GMOs because the modifications could also be generated through conventional mutagenesis techniques (Laaninen 2016). Part of the agribusiness industry held that CRISPR products should be excluded from GMO legislation, too. The European Seed Association (ESA), for example argued (ESA 2015) that changes induced by CRISPR could occur naturally, and that subjecting CRISPR-generated products to GMO legislation would hamper the business prospects of European plant breeding companies and push research to relocate elsewhere.

The European Parliament also started to pay attention to more prudential views. A briefing of the Scientific Foresight Unit of the Panel for the Future of Science and Technology (STOA) – a research and assessment unit established in 1987 – in May 2016 highlighted that various entities had raised concerns with the potential dangers and hazards of CRISPR to consumers and to the environment (Laaninen 2016). Government agencies such as, for example the German Federal Agency for Nature Conservation and the Environmental Agency Austria argued that the new plant breeding techniques could pose environmental risks and should, therefore, be subjected to GMO regulations. Part of the agribusiness industry raised similar concerns. For example in January 2015 various NGOs – including, for example Greenpeace and Econexus – wrote to the Commission that new breeding technologies should be subjected to GMO legislation on the basis of the precautionary principle because of lack of information to assess the risks posed by new technologies. In December 2015, IFOAM EU – a European organization for organic food and farming – called for subjecting plants bred through new technologies to the same risk assessment, mandatory traceability, and obligatory labeling requirements that apply to GMO products.

Additional sources of concern increased the sense of threats posed by CRISPR. In October 2016, Member of European Parliament (MEP) Maria Heubuch asked what the Commission aimed to do to prevent spontaneous and non-authorized transboundary movements of gene-drive modified organisms (i.e. those modified organisms that can pass genetic alterations through generations), which would be regarded as GMO and subjected to the Cartagena Protocol on Biosafety to the Convention on Biological Diversity. In September 2017, MEP Anja Hazekamp posed the question to the Commission about what could be done with the Member States that aimed to derogate the use of CRISPR and other new genetic engineering techniques, running contrary to the precautionary principle – to which the Commission replied that they would not undertake any actions to orient the use of CRISPR insofar as initiatives carried out within the Member States were regarded in accord with EU legislation. Broader concerns toward new technologies were also expressed, in December 2017, by a Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee, and the Committee of the Regions, which addressed, among others, the issues of commercially available "do-it-yourself" bio-kits for the production of genetically modified microorganisms, possible intentional bio-attacks, and accidental contaminations with modified viruses or bacteria.

While no policy initiative was undertaken by either the EU Parliament or the Commission, a juridical case helped shape European policy orientation toward CRISPR. Following a dispute between the *Confédération paysanne* and others on the one hand, and the French Prime Minister and Minister for Agriculture, the Food Processing Industry and Forestry on the other one, in 2016 the French government asked the European Court of Justice (ECJ) to clarify whether organisms obtained through the new breeding techniques should be subjected to GMO approval process. On 25th July 2018, the ECJ ruled (Case C-528/16) that the new breeding techniques – including CRISPR – should be regulated as GMOs and, therefore, subjected to review, traceability, labeling, and monitoring for commercial purposes.

The ruling of the ECJ sparked an animated debate (Gelinsky & Hilbeck 2018). The ECJ had argued that the application of Directive 2001/18 to CRISPR was justified on the basis of the precautionary principle, also taking into account the risk that genetic modifications released into the environment could spread across the boundaries of the Member States. Part of the agriculture sector and NGOs welcomed the ECJ's decision because of concerns that patented gene-edited organisms would supplant the seeds owned by incumbent farmers and that the consumers would need to be informed of the genetic manipulation of foodstuff. Part of the agribusiness industry, instead, held that organisms created through CRISPR could be obtained – albeit less efficiently – also with conventional breeding techniques, and that they did not contain alien genes like in the organisms that are generated through mutagenesis techniques. The Group of Chief Scientific Advisors of the Commission joined the dispute by declaring, in November 2018, that the ECJ ruling was a setback for cutting-edge science and innovation in the EU and by recommending that the GMO directive is reviewed "to reflect current knowledge and scientific evidence, in particular on gene editing and established techniques of genetic modification" (EU Group of Chief Scientific Advisors 2018, p. 6). Some European Members of Parliament also called, in January 2019, for a revision of the GMO directive or an introduction of exemptions to include the new technologies for gene editing.

Various actions followed the ECJ ruling to ban CRISPR products in the EU. The Commission was especially busy on two fronts, namely tackling experimental cultivations of crops in the EU that used CRISPR products and preventing the imports of CRISPR products into the EU market. On the cultivations front, the Commission called Member States to abide by the ECJ ruling, which threw a number of cultivations that had been permitted in Sweden, Belgium, and the UK into uncertainty (EU Commission 2018a,b). On the imports front, the Commission recommended that Member States strengthen border controls, also in accordance with the UN Cartagena Protocol on Biosafety to the Convention on Biological Diversity. The Policy Department for Citizens' Rights and Constitutional Affairs Directorate-General for Internal Policies of the Union, however, acknowledged in April 2019 that border controls would not be able to identify and track CRISPR and other products created with the new technologies, which could be able to enter the EU market undetected and unlabelled (PE 608.871).

Further concerns about CRISPR specifically arose around the possibility to use this technology on human embryos. Since the Council of Europe promoted the European Convention on Human Rights and Biomedicine (the "Oviedo Convention") in 1997, many EU Member States banned the creation of human embryos for research purposes although a few of them, most notably Germany and the UK, did not sign it. Research that leads to the modification of the genetic heritage of human embryos or to the destruction of human embryos was not funded by EU programs – most notably, Horizon 2020. Despite such lack of public support, experimentation with CRISPR on human embryos started to take place, precisely in the UK wherein 2016 the Human Fertilization and Embryology Authority approved research on in vitro fertilization using human embryos for up to seven days before they were destroyed.

6. Discussion: Explaining tendencies and variety of regulatory responses to CRISPR

The regulatory responses to the rise of CRISPR in both the US and the EU look far from a rational and linear process (Braybrooke & Lindblom 1963; Hofer and Schendel 1978). CRISPR-related policy problems – from the impact on national security to the one on agribusiness – were paid attention in a fragmented way rather than in a comprehensive approach; existing regulatory institutions –especially the Coordinated Framework in the US and the GMO directive in the EU – provided sources of default regulatory responses; and regulatory options were contemplated while also taking into account partisan interests – for example those of large agribusiness rather than those of organic food and farming operators. In addition, the formulation of regulatory responses took place

within conditions of uncertainty about the future trajectory of CRISPR development, about the effects of CRISPR on stakeholders' organizations, and of the impact of regulatory responses on CRISPR developments.

There are some similarities in the way uncertainties played a role in the development of regulatory responses to CRISPR in the US and the EU. In both contexts, the rise of CRISPR posed state uncertainty about the nature of the emerging technology (especially whether CRISPR is different from existing genetic engineering techniques), effect uncertainty about CRISPR impact on such diverse areas as plant breeding, national security, and self-inflicted personal harms, and response uncertainty about the appropriateness of using existing regulatory institutions for CRISPR applications rather than adjusting regulations to CRISPR features. Response uncertainties included, for example considerations that too restrictive regulations could harm domestic business while too permissive regulations could result in unwelcome effects, like, for example the introduction of food products that pose threats to the health of consumers. Table 2 illustrates issues that state, effect, and response uncertainty posed in the component parts of the pre-decisional stage of the regulatory development process of CRISPR. Uncertainty plagued, in different ways, the definition of CRISPR-related policy problems, the identification of alternative courses of action, and the appraisal of options available.

The two cases also exhibit some striking differences. In the US, the Federal Government launched a review of the existing regulatory system that resulted in the Update to the Coordinated Framework, while in the EU the ECJ ruled about the applicability of the existing GMO directive to products obtained through the CRISPR process. Related differences arose between the relative tolerant (in the case of FDA) or permissive (in the case of USDA and EPA) stance toward CRISPR products in the US, and the restrictive policies to curb CRISPR-based cultivations in the EU and to block the import of CRISPR products into the EU market. A question arises, then, concerning what explains the different regulatory responses in the US and the EU?

Relatively similar issues were confronted in the US Congress and in the EU Parliament concerning how CRISPR should be regulated. Existing regulatory institutions played a different role to cope with the uncertainty posed by CRISPR technology, instead. In the US, existing regulatory institutions were reviewed and related regulatory practices adjusted while taking into account expectations about future CRISPR developments (further adjustments may take place after the scientific community called for additional improvements to the regulatory system following the issue of the Update to the Coordinated Framework). Figure 2 provides a pictorial representation of the CRISPR regulatory response model in the US, where the link (a) indicates the anticipation of issues about the launch of CRISPR applications, link (b) indicates the anticipation of issues about the application of adjusted regulations to CRISPR products, and link (c) indicates the anticipation of issues arising from the

Table 2 Issues that sources of uncertainty posed in the component parts of the pre-decisional stage of the regulatory development process of CRISPR

Component parts of the pre-decisional stage	Types of uncertainties		
	State uncertainty	Effect uncertainty	Response uncertainty
Definition of policy problems	What opportunities and threats are posed by CRISPR in such areas as national security, agribusiness, and biohacking?	How does CRISPR affect the role and performance of regulators? Who is in charge of regulating CRISPR products and how, among existing regulatory agencies?	How would a regulatory response affect the development of CRISPR applications?
Scan of the alternatives	Should CRISPR be banned? Should it be regulated, and how? Should the development of CRISPR be supported through public funding?	Should existing regulations apply to CRISPR products? Alternatively, what other regulation should apply to them?	Who will invest in the CRISPR technology? Which applications will be developed?
Appraisal of the options available	What are the advantages of CRISPR for business, for consumers, for the national economy?	What are the merits of regulating CRISPR by existing standards? What, instead, are the merits of adjusting existing regulations?	What are the benefits of the adjusted regulation for developing CRISPR applications?

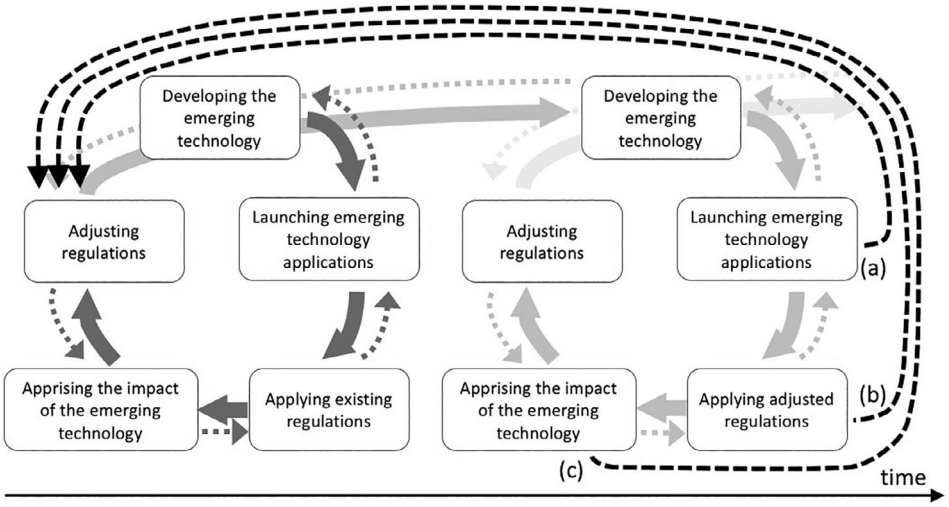

Figure 2 The development of regulatory responses to CRISPR technologies in the US with consequential linkages (solid bold arrows) and anticipatory linkages (dotted thin arrows). Anticipatory links (a), (b), and (c) indicate that expectations about future technological development and its impact affected the regulatory response to CRISPR.

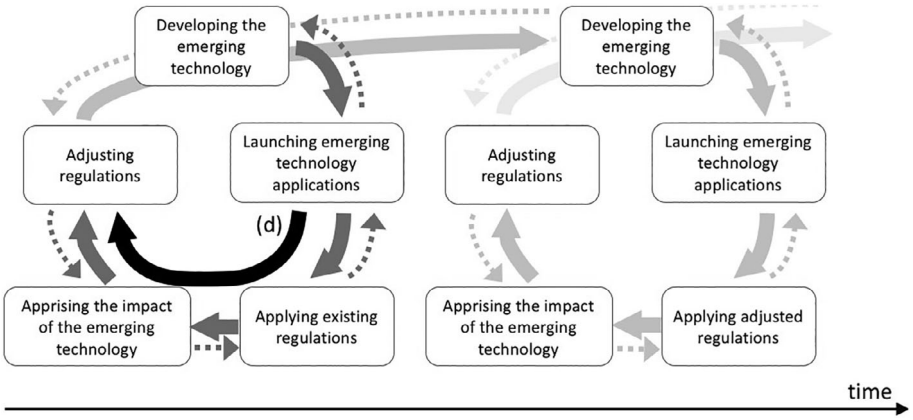

Figure 3 The development of regulatory responses to CRISPR technologies in the EU with consequential linkages (solid bold arrows) and anticipatory linkages (dotted thin arrows). Consequential link (d) indicates that the rise of CRISPR triggered a regulatory response in the form of reaction by existing regulatory standards.

appraisal of the impact of CRISPR once the adjusted regulation is implemented. In the EU, instead, existing regulatory institutions were applied to CRISPR applications following the pronouncement of the ECJ. Figure 3 provides an illustration of the CRISPR regulatory response model in the EU, where the link (d) indicates regulatory adjustment as a consequential action to the launch of CRISPR applications. Differently from the US, the EU tackled the state, effect and response uncertainty about CRISPR by subjecting the new technology to existing regulatory institutions rather than undertaking any institutional review and adjustments of regulatory practices.

The analysis of the cases of regulatory responses to CRISPR in the US and the EU suggests some hypotheses around the proposed model shown in Figure 1. First, anticipatory and consequential linkages may exert their influence on previous and subsequent activities that may not be immediately adjacent. Depending on how farsighted individuals are, they would anticipate future trajectories of technological and regulatory development when coping with the uncertainty that arises from the emerging technology and devising regulatory responses. Existing regulatory institutions, instead, play an important role to affect consequential activities. Second, regulatory development may depend on the relative strength of anticipatory and consequential linkages. If anticipatory linkages are more dominant than consequential ones, then regulatory development would include responses to expected future technological development and its impact. If consequential linkages are more dominant than

anticipatory ones, then regulatory development would mainly consist of a reaction to emerging technology by existing regulatory standards. Which linkages prevail would depend on local circumstances that affect which options are contemplated, how much consideration they receive, and whether they fit with the interests and values of influential stakeholders and decision-makers.

7. Conclusions

This study provides a theoretical account of regulatory responses to emerging technologies based on the cases of regulatory development after the rise of CRISPR gene-editing technology in the US and the EU in 2012–19. Regulatory responses to emerging technologies can be understood as developing in a gradual and iterative fashion, where sequential cyclical activities are connected by anticipatory and consequential linkages. In addition, regulatory responses to emerging technologies are exposed to the source, effect, and response uncertainty, which affect the expectations that individuals hold toward future technological and regulatory developments. The regulatory response to emerging technologies is also affected by existing regulatory institutions, which help account for different trajectories of regulatory development across countries.

This study suggests a couple of ways to amend theories of regulatory development and make them better equipped to account for the regulatory response to emerging technologies. First, theories of regulatory development should depart from approaches that posit sequences of stages (Bernstein 1955). Under conditions of uncertainty about the nature and effects of emerging technologies, as well as of the consequences of regulatory responses, regulatory development is better understood as sequences of cyclical activities where regulatory responses are progressively adjusted over time, which can be understood as a specification of the "common trajectory or pattern of regulatory action" posited by Howlett *et al.* (2020). Successive regulatory adjustments would react to evidence of technological development and anticipate future technological advances, which would also depend on expected reactions to the same regulatory response. Depending on how farsighted individuals are, regulatory adjustments would take into account future trajectories of technological and regulatory development. In the absence of a regulatory policy-making initiative, however, regulatory responses may largely consist of the repurposing of existing regulatory standards.

Second, theories of regulatory development should also depart from approaches that posit the creation of novel regulations tailored to emerging technology. Uncertainty about the nature and effects of emerging technologies as well as about the consequences of regulatory responses entails that actors may not be capable to formulate accurate accounts of regulatory problems and design appropriate regulatory solutions. In such circumstances, existing regulatory institutions provide sources of default regulatory responses before alternative options can be considered, once actors gain a better understanding of the possible technological applications and their effects. Theories of regulatory development, therefore, should include the possibility that policy-makers remain passive toward the rise of emerging technologies while they "wait and see" the effects of the application of existing regulatory institutions.

The empirical part of the study also throws some light onto the regulatory responses to CRISPR gene editing technologies in the US and the EU, in particular. In the US, the Update to the Coordinated Framework and subsequent adaptation in the conduct of the federal regulatory agencies resulted in a relatively tolerant and permissive regime toward CRISPR products. In the EU, instead, the ECJ ruling and following enforcement actions of the Commission resulted in a relatively restrictive regime toward CRISPR applications. Critiques from the scientific community and the industry suggest, however, that the regulatory responses in both the US and the EU are unfinished business. Appraisals of the impact of future developments of CRISPR may likely stimulate further regulatory adjustments to cope with novel CRISPR applications that question the advantageousness of the current regulatory institutions.

This study has implications for research on the design of effective governance systems of emerging technologies. Policy-makers and regulators should appraise the impact of existing regulations on the development of emerging technologies and adjust regulations while anticipating their consequences on further technological developments. Consultations with experts and stakeholders provide valuable inputs to develop the foresight capacity required to anticipate future trajectories of technological development and applications. Inaction from the side of policy-makers and regulators, instead, could result in subjecting the emerging technologies to existing

regulations, which may be unsuitable or inadequate to reap the opportunities that arise from technological breakthroughs. Within the global context, different regulations of emerging technologies may have important repercussions on relative productivity, competitiveness, the attraction of capital and talents, and growth.

Finally, this study has some limitations that should be acknowledged. The proposed model does not explain whether regulatory responses consist of adjustments to regulations rather than abrupt radical changes to the existing regulatory system. It seems plausible that there are limits in the extent to which existing regulatory institutions can be stretched to accommodate the regulation of emerging technologies and their applications, but further research is needed to account for regulatory reforms that come out with novel regulatory institutions that better fit the nature and effects of emerging technologies. In addition, the empirical part of this study should be expanded with the inclusion of further country cases and kinds of emerging technologies to increase evidence of a variety of regulatory responses.

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