Erasmus School of Law

Grey Areas in the Regulation of Green and Red Biotechnology

Towards robust legislation for rapid technological change

Lonneke Poort

Willem-Jan Kortleven

with assistance from Evert Stamhuis

Erasmus University Rotterdam

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Client:	Netherlands Commission on Genetic Modification (COGEM) P.O. Box 578 3720 AN Bilthoven, Netherlands Contact person: Martine Boonk, Coordinator, Subcommittee on Ethical and Societal Aspects Martine.boonk@rivm.nl
Contractors:	Lonneke Poort Willem-Jan Kortleven assisted by Professor Evert Stamhuis, LLM Erasmus School of Law, Department of Law & Markets and Department of Law, Society & Crime Erasmus University Rotterdam P.O. Box 1738 3000 DR Rotterdam Contact person: Dr Lonneke Poort Poort@law.eur.nl
Supervisory committee:	Professor Paul Struik (chair) Martine Boonk (secretary) Marie-Louise Bilgin Lucien Hanssen Pepijn Naus Clara Posthuma
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Foreword

Scientific and technological advances in biotechnology are proceeding at a rapid pace and innovations are often quick to appear on the market. These must first pass a thorough assessment of their implications for human and environmental safety, for which there is an extensive body of legislation at the national and supranational levels. Aspects such as genetic modification (COGEM's field of expertise) can be particularly complicated and are often sensitive in the public sphere. The relevant legislation are EU directives on contained use and on the deliberate release into the environment of genetically modified organisms.

However, the regulatory regime cannot always keep up with scientific and technological changes, particularly for developments in biotechnology. This leads to problems in practice: grey areas arise where existing regulations are inadequate or where it is not clear whether or not a new technology involves genetic modification, while desirable innovations can be delayed unnecessarily.

In view of this, COGEM commissioned a study to investigate these grey areas and identify ways in which the legal and regulatory framework can be made more robust than it is at the moment. In this context, 'robust' can be interpreted as future-proof and an ability to adapt to scientific, technological, societal and possibly even political developments. A team of researchers at Erasmus School of Law carried out the study. COGEM appointed a supervisory committee consisting of representatives from the COGEM secretariat, the COGEM Executive Board, the Ministry of Infrastructure and Water Management and the ministry's GMO Office.

This is the final report of the research project 'Grey areas in the regulation of green and red biotechnology: towards robust legislation for rapid technological change.' The researchers set out to explore the grey areas mentioned above and the possibilities for making the regulatory regime more robust, while providing a legal and juridical basis for putting these into practice.

Following a brief introduction, the authors present a theoretical framework for investigating legislative grey areas and the robustness of the regulatory regime. They then describe a number of building blocks for different regulation strategies. Following a methodological chapter on the empirical part of the study, the authors analyse two contrasting case studies: one in 'green biotechnology' (the DuRPh programme on the use of cisgenesis to create potato varieties resistant to potato blight caused by the oomycete *Phytophthora infestans*) and one in 'red biotechnology' (the development of self-amplifying mRNA vaccines).

In these case studies, practitioners in the field of biotechnology were asked about their experiences with and interpretation of the robustness, or lack of it, of the legal framework and the legislative changes they would like to see (to increase its robustness).

In the final chapter, the authors interpret their findings from the case studies according to the theoretical framework and draw conclusions concerning the options for making the legal and regulatory framework more robust.

The supervisory committee has determined that the final report meets the stated objectives. The report provides an in-depth analysis of the problem and possible solution strategies, while the case studies – together with the relevant sectors – explore just how much regulatory robustness is required and is feasible in practice.

The supervisory committee is convinced that this report will prove to be valuable for COGEM's work in future, and hope that it will also be of service to readers who are interested in how

regulatory and enforcement agencies and advisory bodies are struggling with the growing number of gaps between the regulatory framework and scientific, technological and societal developments.

Lastly, I would like to thank the members of the supervisory committee for the expert way in which they commented and advised on the plans, ideas and reports of the research team. I would also like to thank the authors for their constant dedication, openness, expertise and diligence. The five meetings we had together were lively, informative and productive.

The opinions and visions expressed in this report are those of the authors and not the supervisory committee or COGEM.

Paul C. Struik

Chair of the supervisory committee

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List of abbreviations

ATMP	advanced therapy medicine products
BSO	biological safety officer
CAT	Committee for Advanced Therapy
CBD	*Commissie Biotechnologie bij Dieren* / Committee on Animal Biotechnology
CCMO	*Centrale Commissie Mensgebonden Onderzoek* / Central Committee on Research Involving Human Subjects
CHMP	Committee for Medicinal Products for Human Use
CJEU	Court of Justice of the European Union
COGEM	Netherlands Commission on Genetic Modification
DG	Directorate-General
DNA	deoxyribonucleic acid
DuRPh	*Duurzame Resistentie tegen Phytophthora* / Sustainable Resistance to *Phytophthora*
EFSA	European Food Safety Agency
EMA	European Medicines Agency
ESF	environmental safety officer
EU	European Union
GMO	genetically modified organism
Gwwd	*Gezondheids- en welzijnswet voor dieren* / Health and Welfare of Animals Act
IenW	Ministerie van Infrastructuur en Waterstaat / Ministry of Infrastructure and Water Management
LNP	lipid nano particle
LVVN	*Ministerie van Landbouw, Visserij, Voedselkwaliteit en Natuur* / Ministry of Agriculture, Fisheries, Food Security and Nature
METC	medisch-ethische toetsingscommissie / Medical Ethical Review Committee
mRNA	messenger RNA
NGT	New Genomic Techniques
NVCGT	Netherlands Society of Gene and Cell Therapy

RIVM	National Institute for Public Health and the Environment
RNA	ribonucleic acid
samRNA	self-amplifying messenger RNA
ScL	Subcommittee on Agriculture
ScMV	Subcommittee on Medical and Veterinary Aspects
TFEU	Treaty on the Functioning of the European Union
UMCG	University Medical Center Groningen
US	United States
VOV	*vergunning onder vaste voorwaarde* / authorisation with standard conditions
VRP	viral replicon particle
VWS	*Ministerie van Volksgezondheid, Welzijn en Sport* / Ministry of Health, Welfare and Sport
WMO	*Wet medisch-wetenschappelijk onderzoek met mensen* / Medical Research Involving Human Subjects Act
WUR	Wageningen University & Research

Summary

Background

It is well-known that legislation can be overtaken by advances in science and technology. We see this in biotechnology, and more specifically in genetic modification, where the regulatory regime does not always keep pace with rapid technological change. Regulations can also become less than adequate in the face of societal change. As a result, grey areas are inevitable, giving rise to uncertainty about the scope and interpretation of European and national regulations on genetically modified organisms (GMOs). Underlying this is the ongoing need to find the right balance between ensuring safety and facilitating innovation. Regulations that are insufficiently compatible with new developments may allow potentially risky technological applications to escape regulation, but may also unnecessarily hamper innovation. COGEM (the Netherlands Commission on Genetic Modification) observes that current GMO regulations are too far out of step with new technological developments, which compromises safety, hampers innovation or both. In view of this, COGEM asked the Erasmus School of Law to study the emergence of grey areas and explore possibilities for structuring legislation so that it can keep up with rapid technological developments. In other words, how can the regulatory regime be made more robust?

Approach

The research involved a theoretical exploration of the problem of grey areas and the possibilities for developing a more robust regulatory regime (Part I), followed by two case studies in which we investigated how a lack of robustness affects the regulation of biotechnology in practice (Part II). The findings from the case studies were then combined with the theoretical analysis to identify the feasibility and challenges of potentially fruitful solution strategies (Part III).

Part I From grey areas to robust regulation

To obtain a better understanding of grey areas we explored the concept of *regulatory disconnection*. This refers to uncertainties about which rules apply to new technological applications and/or situations where the applicable rules are perceived to be either too strict or too permissive. Many technology regulations have a dual objective: to protect public interests, such as public health and the environment, and to promote innovation. This can be seen in both Dutch and European Union (EU) GMO legislation. A regulatory regime that does not accommodate new technological developments is likely to fall short in protecting public interests and/or promoting innovation. Moreover, the complexity involved in regulating technology is broader than just the tensions between safety and innovation. Considerations and values from knowledge domains other than technology and law, such as economics, ethics and societal knowledge, must also be taken into account.

In exploring grey areas and identifying fruitful solution strategies, this report highlights the importance of the political, societal, economic and ethical context in which the problem of regulatory disconnection arises. This accords with an interactive approach to law. In an interactive approach, regulation can also have a communicative or symbolic function in which legal standards provide a framework for further communication: the development of legal standards and frameworks interacts with technological and societal change. This takes account of both the reality of technological dynamics and (ongoing) political and public debates.

Given the dynamics in science and technology, legislation is needed that is capable of *regulatory reconnection* to limit regulatory disconnection. Robust regulation meets this challenge. In this report, robust regulation is defined as *regulation that can address technological and scientific developments in a timely and legally robust manner in order to protect public interests and promote (or at least not unnecessarily hamper) innovation*.

Where new technological or scientific developments threaten to cause regulatory disconnection, two strategies are often seen in response: *stretching* and *breaking*. The first strategy involves maintaining the existing regulations, but interpreting legal definitions in such a way as to accommodate the new developments. The second strategy comes into play when the stretching strategy is considered to be unfeasible or undesirable, and involves changing or replacing the existing regulations. The choice of strategy is influenced by arguments from various fields of knowledge.

The *stretching* and *breaking* adaptation strategies serve as the basic templates for all attempts to make the regulatory regime more robust. The building blocks for robust regulation discussed in this report take one of these strategies as their starting point: they either focus on increasing the 'stretching capacity' of the rules, or they aim to make the rules easier and quicker to amend. Sometimes, the two strategies are combined. The building blocks can be divided into four categories: abstract formulation of legislation; temporary and experimental legislation; judicial law-making; and regulation by regulatory agencies. Each of these building blocks is evaluated in the light of the question 'To what extent can this solution contribute towards a regulatory regime that can address technological and scientific developments in a timely and legally robust manner to ensure public and environmental safety and promoting (or at least not unnecessarily hampering) innovation?'

Part II Challenges and needs in the regulation of biotechnology

The first case study concerns the use of cisgenesis in agriculture ('green biotechnology'). The DuRPh project, which ran from 2005 to 2015, studied the use of cisgenesis to create varieties of potato resistant to *Phytophthora* blight by inserting genes from a wild-type potato variety. As no foreign DNA is introduced in this process and the same results could, in principle, also be obtained through conventional breeding methods, the question is whether or not such applications should be exempted from the scope of EU GMO legislation. This case is set against the backdrop of the EU legislative proposal for new genomic techniques (NGTs), which distinguishes between category 1 NGT and category 2 NGT. In this proposal, crops falling under category 1 NGT would be treated as equivalent to conventional crops and exempt from the GMO authorisation regime, while category 2 NGT crops would be subject to a more flexible regime if certain sustainability criteria are met. According to the latest developments, cisgenic crops could fall under category 1 NGT, but this remains uncertain until political agreement is reached on the proposal.

The second case study concerns the development of self-amplifying messenger RNA (samRNA) vaccines ('red biotechnology'). Regular mRNA vaccines are not covered by the GMO legislation because mRNA is not considered an organism and thus cannot be classified as a genetically modified organism. SamRNA vaccines, however, have the ability to replicate within the cell, which technically speaking brings them within the scope of EU GMO legislation. This raises

questions about the definitions of an organism and a GMO. What qualifies as an organism or a biological entity? What is the relevance of the ability to replicate for the scope of the law? This case is set against the backdrop of a reform of EU pharmaceutical legislation, which aims to harmonise and centralise regulation.

In the case studies, two forms of regulatory disconnection can be identified. The first form of regulatory disconnection arises as a consequence of the precautionary regulation under the GMO legislation, which is considered by stakeholders in both cases to be more burdensome or restrictive than justified by the protection goal of the legislation (over-inclusive regulation).

The second form of regulatory disconnection is caused by the legal uncertainty of the applicability and scope of the GMO status. Both cisgenic crops and samRNA vaccines were developed after the adoption of the legal definition of a GMO, and neither innovation could be unambiguously classified as a GMO or a non-GMO. For cisgenesis, this ambiguity has been resolved by subsequent case-law, although the NGT proposal may create new ambiguity. For samRNA vaccines, the legal uncertainty remains, partly as a result of disagreement between experts, EU member states and the European Commission about the applicability of the legal criterion 'ability to replicate', which is part of the GMO definition. Does this criterion refer exclusively to vaccines that can spread outside the host cell, or does it also apply to vaccines that only replicate within the host cell? This distinction is important because spreading outside the cell presents greater safety risks.

In response to the perceived regulatory disconnection, four needs can be distilled from the case studies: 1) the desire among a significant section of scientists and the industry to ease administrative burdens and obstacles resulting from the GMO legislation; 2) the desire among other stakeholders to pay due attention to safety and precautionary considerations and/or ethical considerations, which according to some respondents can only be guaranteed by having a separate regime for GMOs; 3) the need for legal clarity; and, associated with that, 4) the need for faster and shorter revision procedures when the legislation requires amending.

Based on these needs, we reflect on the building blocks for robust regulation to identify their possible advantages and disadvantages and the feasibility of putting them into practice.

Part III Building blocks for robust regulation

Abstract formulation of legislation can address the first need, easing the administrative burden, and the fourth need, adaptivity. Some respondents suggested a **product-based approach**. The advantages of this approach are that there would be no specific obligations for GMOs and it would be easier to accommodate new technologies (need 4). At the same time, however, this approach imposes additional obligations on non-GMOs, which is at odds with the desire to ease the administrative burden (need 1). Neither can this approach accommodate the desire among some stakeholders for a separate regime for genetically modified products based on safety, precautionary and/or ethical considerations (need 2). Furthermore, a product-based approach poses political, social, legal and policymaking difficulties.

However, abstract formulation of legislation is also possible without a product-based approach. **Abstract provisions in legislation** work best **in combination with delegation to regulatory agencies**. Less detail makes regulations less prone to becoming outdated. A disadvantage is

that abstract provisions provide less direction and clarity. Delegation through various levels makes regulation more difficult to understand, which creates tension with the third need. It also allows for less control by the institutions of representative democracy.

For legislation that is difficult to amend, one option is **derogation** through new legislation. The NGT legislative proposal is an example of this. The disadvantage is that exceptions and anomalies make regulation harder to comprehend.

Regulation by regulatory agencies can contribute to greater regulatory adaptivity (need 4). Regulatory agencies are better able than the legislature to reconcile adaptivity and legal certainty (needs 4 and 3). Possible disadvantages are that depoliticisation makes the democratic trade-off between protecting public interests and promoting innovation more difficult (definition of robust regulation), with the risk that social and ethical aspects may be insufficiently taken into account (need 2). In general, this option depends on the latitude in the legislation.

Delegation to regulatory agencies can take place at the member state level or at the EU level. **Delegation at the member state level** has several advantages. For one thing, national agencies are best able to tailor regulation to the situation in their respective member state. They may also be able to adapt regulation more quickly than EU agencies (need 4). Furthermore, delegation to the member state level better addresses the desire for control by member states and their agencies. However, the disadvantage is that this can lead to differences in the interpretation of EU legislation, which may undermine the need for legal clarity (need 3). It can also create tension with the EU principle of the single market.

Delegation at the EU level has different advantages. Centralisation can promote legal clarity (need 3) and reduce administrative burdens by integrating cumulative procedures (need 1). The disadvantage is that regulatory agencies at the EU level may be less adaptive than national agencies (need 4). Additionally, there may be resistance from member states to surrendering powers.

Temporary and experimental regulation contributes to the adaptivity of regulation (need 4). **Temporary legislation** may be adopted more quickly because its temporary nature makes it easier to reach consensus. Temporary provisions also require regular evaluation, revision or extension, which further strengthens adaptivity. A disadvantage is that failure to reach agreement on future arrangements when temporary provisions expire creates legal uncertainty (need 3). Moreover, the political feasibility of using this building block is questionable as legislative actors within the EU tend to make laws that are tightly formulated to bind each other and future legislators strictly to the provisions.

Experimental regulation, such as regulatory sandboxes, makes it possible to get to grips with the 'unknowns' of new technological applications and (alternative) regulation of these applications by gaining practical know-how on a limited scale. This can be beneficial for both the need to protect public interests (need 2) and the need to promote innovation (need 1). A potential disadvantage is that a more favourable regime for experimenting businesses creates legal inequality and legal uncertainty. Moreover, exceptions to the rules may reduce the level of protection of public interests (need 2) and make regulation harder to comprehend (need 3). Experiments also require a clear division of responsibilities between the regulatory agency and

the experimenting business. Such a division is difficult to achieve, and the necessary safeguards may be administratively burdensome (need 1).

Judicial law-making can also contribute to more robust legislation. Judges can provide more adaptivity than the legislature. They can also address the need for legal clarity (need 3) and ensure legal robustness (legal equality and legal certainty). However, the degree of adaptivity largely depends on the highest courts, at the EU level the Court of Justice of the European Union. This route takes a long time and significant hurdles need to be overcome. Moreover, the position of the judge is less suited to balancing conflicting social desires, values and interests. Effecting change through judicial law-making is generally a gradual process.

The various building blocks have advantages and disadvantages, as summarised above. Not all advantages and disadvantages carry the same weight, nor do they have the same significance in every context. Therefore, it is important to assess the potential contribution of different building blocks and their drawbacks on a case-by-case basis and, based on this, determine the best combination, form and dosage of building blocks to be used. Based on our research, we conclude that the following building blocks have the greatest potential for creating a robust regulatory regime, preferably used in combination:

1. the use of more abstractly formulated rules in legislation that are less likely to be overtaken by new developments (or, if necessary, bypassing detailed and static rules through derogation);
2. regulation by regulatory agencies with an adequate mandate to quickly adapt these regulations to new developments;
3. temporary or experimental provisions in legislation or lower regulations, which can serve as a lever to ensure regulations are actually adapted to new developments.

Some of these building blocks are already being used, especially the second one, but there is room to make much greater use of all three, possibly in new ways as well. In short, we see opportunities to make the regulatory regime more robust. Which options will be the most appropriate will depend on the specific context and requires further reflection and political choices.

1 Introduction

1.1 Reason for the study

It is well-known that legislation can be overtaken by advances in science and technology. We see this in biotechnology, and more specifically in genetic modification, where the regulatory regime cannot always keep up with rapid technological change. Nor is it always possible to anticipate unknown developments in society. As a result, it is inevitable that grey areas arise where there is uncertainty about the scope and interpretation of European and national laws and regulations on genetically modified organisms (GMOs). This raises the question of how to deal with such grey areas.

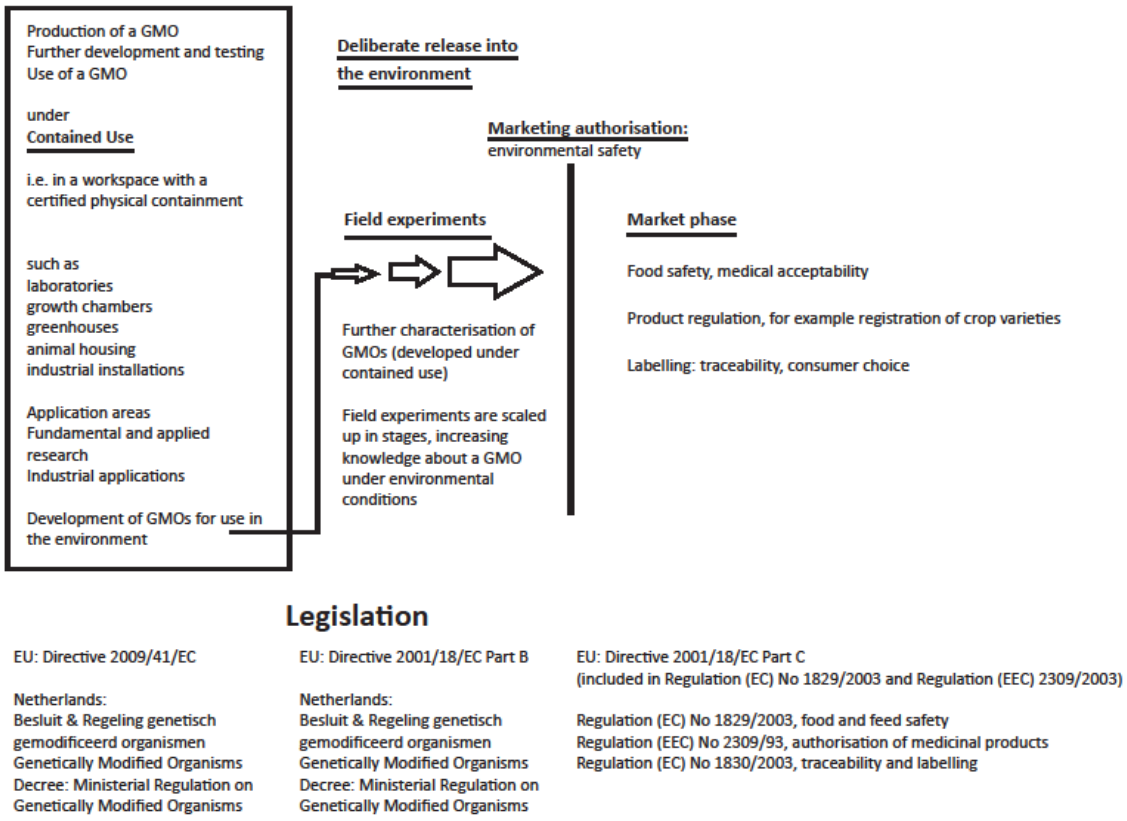
In the European Union (EU) the various phases of research and application of genetic modification are mostly regulated by two EU directives: one on contained use (2009/41/EC) and one on the deliberate release into the environment of genetically modified organisms (2001/18/EC). An important objective of both directives is to ensure public safety through the use of an authorisation procedure for work with GMOs. EU legislation allows member states to adopt their own rules for contained use and for the deliberate release of GMOs for non-commercial purposes, such as field trials and clinical trials. These rules must prioritise safety issues by means of an environmental risk assessment. Decisions on the placing on the market of GMOs are taken at the European level (see Figure 1.1 for further details). The environmental risk assessment is also central to this process.

Current technological advances are making it increasingly difficult to determine whether new biotechnological applications should be considered to be GMO applications or not. Underlying this is the ongoing need to find the right balance between ensuring safety and facilitating innovation. Laws and regulations that are insufficiently compatible with new developments may allow potentially risky technological applications to escape regulation, but may also unnecessarily hamper innovation. The Netherlands Commission on Genetic Modification (COGEM) observes that current GMO regulations are too far out of step with new technological developments, compromising safety, hampering innovation, or both. In view of this, COGEM decided to commission a study to obtain a better understanding of how grey areas arise and more insight into how the current legal and regulatory framework can be structured to keep pace with rapid technological developments. In other words, how can the regulatory regime be made more *robust*?

1.2 Purpose of the study

This study takes stock of the legal options for making the regulatory regime more robust. It provides insight into the feasibility of putting these into practice by reflecting on existing needs for robustness and the difficulties experienced with the authorisation procedures. The study starts with a theoretical analysis of robust legislation and an analysis of the grey areas that arise in biotechnology. In this report, we marry theoretical insights on robust legislation with practical experience to create building blocks for a robust regulatory regime.

Figure 1.1 Schematic representation of the GMO legislation for different application areas[1]



1.3 Scope of the study

This study consists of a theoretical exploration of the problem of grey areas and the options for a more robust regulatory regime, followed by two case studies in which we explore in concrete terms how the lack of robustness affects the regulation of biotechnology. These two case studies have different backgrounds (agriculture and medical applications) where different political and societal values come into play. This means that the legal possibilities must be explored within these two specific contexts. To give as varied as possible picture of the different contexts and complexities within biotechnology, we chose case studies from green biotechnology and red biotechnology. The first case study concerns the use of cisgenesis in agriculture (green biotechnology). The DuRPh project, which ran from 2005 to 2015, investigated the use of cisgenesis to create varieties of potato resistant to *Phytophthora* blight by inserting genes from a wild-type potato variety. As no foreign DNA is introduced in this process and the same results could, in principle, also be obtained through conventional breeding methods, the question is whether such applications should fall within the scope of the EU GMO legislation. Cisgenesis currently falls under the GMO legislation, but this is subject to considerable debate.

The second case study concerns the development of self-amplifying messenger RNA vaccines (samRNA vaccines). Regular mRNA vaccines are not covered by the GMO legislation because mRNA is not considered an organism and thus cannot be classified as a genetically modified organism. SamRNA vaccines have the ability to replicate within the cell (see Chapter 6), which

[1] Taken from Bergmans, Poort & Kleinjans, 2016, p. 31.

technically speaking brings them within the scope of the EU GMO legislation. This raises questions about the definitions of an organism and a GMO. What qualifies as an organism or a biological entity? What is the relevance of the ability to replicate for the scope of the law? These issues are also hotly debated.

1.4 Structure of this report

This report consists of three parts. Part I is a theoretical analysis of the emergence of grey areas and the possibilities for developing a more robust regulatory regime. This part consists of two chapters (Chapters 2 and 3). Chapter 2 discusses what is understood by the terms 'grey areas' and 'robustness'. Drawing on the literature from multiple disciplines, a theoretical framework is developed to provide a better understanding of the complexity of grey areas and the concept of robust legislation. Chapter 3 draws on a systematic literature study to analyse a number of promising solution strategies for building robustness into the regulatory regime. This reflection combines a legal philosophical investigation with literature from various disciplines, such as regulation theory, sociology of law, public administration and science & technology studies.

Part II begins with a chapter (Chapter 4) that explains the research methods used and the approach taken to the case studies. The grey areas in these case studies were examined and the need for robustness felt by stakeholders investigated through semi-structured interviews, and an analysis of the relevant policy documents, research reports and legal and regulatory framework. This methodological chapter also includes a more detailed explanation of the theoretical framework as an instrument for analysing the findings from the interviews. In the other chapters in this part (Chapters 5 and 6) the theoretical framework is used to explain the findings from the case studies.

Part III links the insights gained from practice (Part II) with the theoretical analysis of the legal possibilities (Part I), focusing on legal and practical feasibility and the potential drawbacks of the solution strategies.

Part I Theoretical analysis

2 Towards a better understanding of grey areas and robust regulation

In this chapter we analyse how grey areas in the regulation of technology can arise as a result of advances in science and technology (§ 2.1) and define what is meant by robust regulation (§ 2.2). We then introduce an interactive approach to robust regulation, which is the guiding principle for the study (§ 2.3).

2.1 Grey areas in the regulation of technology

In Chapter 1, grey areas were briefly introduced as those cases where laws and regulations have not kept pace with technological developments. In the literature, this is called the **pacing problem**.[2] In a setting of rapid technological innovation, legislators and regulatory authorities often have insufficient information and are faced with too much complexity to be able to address new phenomena.[3] But if they wait until more information is available, it may be more difficult to make the necessary regulatory changes because the technology will have become more entrenched. This is called the Collingridge dilemma. The ability to adapt laws and regulations may also be constrained by legal safeguards, statutory provisions, democratic procedures and/or political impasses.[4]

Grey areas caused by the pacing problem can also be defined as situations where there is a **regulation-to-technology disconnection**.[5] Such situations may be caused by **disruptive** technological applications, defined here as innovations that do not fit neatly within existing legal definitions and/or regulatory regimes,[6] or when new knowledge becomes available that shows that certain technological applications are safer or less safe than was thought when the legislation and regulations were adopted. As long as the regulatory framework is not brought into line with such innovations or new knowledge, there will be some confusion about the legal status of new technological capabilities and applications, or regulatory regimes will be found to be either too strict or too permissive. Bennett Moses refers to these situations as '**regulatory regimes** that **may be over-inclusive or under-inclusive**.'[7]

Legal uncertainty and regulatory regimes that are too strict or too permissive can have two main types of negative consequences. On the one hand, both ambiguity and an overly strict regulatory regime may discourage investors and innovators, thereby hampering innovation.[8] On the other hand, both ambiguity and an overly permissive regulatory regime may lead to potentially risky technological innovations slipping through the regulatory net.[9] In such situations of regulatory disconnect there is often a discrepancy between the letter and the spirit of the law. This is because many technology regulations have a dual objective: to protect public interests, such as public health and the environment, and to promote innovation as well.[10] The

[2] Bennett Moses, 2013; Hagemann, Huddleston Skees & Thierer, 2018, p. 58–60; Marchant, 2011; Ranchordás, 2015.
[3] Bennett Moses, 2013, p. 8; Hagemann, Huddleston Skees & Thierer, 2018, p. 55–57.
[4] Marchant, 2011; Hanssen et al., 2018; Ranchordás, 2015. In the American literature the term used for this is 'ossification', see e.g. McGinnis & Wasick, 2014, p. 1040; Nielson, 2018.
[5] Brownsword, 2008, Chapter 6; Du & Heldeweg, 2018, p. 293.
[6] Cf. Kołacz, Quintavalla & Yalnazov 2019, p. 9; Bennet Moses, 2007, p. 275.
[7] Bennett Moses, 2013, p. 7.
[8] See e.g. Bonnin Roca, 2024, p. 3.
[9] Winter, 2024, p. 5.
[10] Cf. e.g. Bonnin Roca, 2024.

Dutch and EU GMO legislation are prime examples. In the EU legislation, this is expressed in the coexistence of the statutory precautionary principle and the innovation principle, which has not yet been established in law.[11] Regulation that does not take new technological development into account is likely to fall short of meeting its protection and/or innovation objectives.

However, this does not mean there is an immediate danger of a legal vacuum arising. Gaps in the technology regulations can be covered by the general safety nets of criminal and civil liability and the protection of fundamental rights.[12] Examples that illustrate this are the criminal complaints filed on behalf of local residents against executives of Tata Steel and Chemours concerning the use of a polluting technology, and the civil climate cases against the Dutch state and Shell under Article 6:162 of the Dutch Civil Code (unlawful act) and Articles 2 and 8 of the European Convention on Human Rights.[13] However, the fact that general law is harder to invoke ex ante than ex post and works on a case-by-case basis reduces the predictability of such proceedings.[14] This can be detrimental to the innovation climate and to safety. The presence of legal safety nets does not therefore alter the fact that, in terms of the above analysis, legal uncertainties and regulatory disconnection may arise.[15]

Box 2.1 Site-directed mutagenesis: from legal uncertainty to legal straitjacket

An example of a disruptive technology leading to legal uncertainty is the development of gene editing techniques (of which CRISPR-Cas is the best known). Because these techniques can be described as 'site-directed mutagenesis', the question arose as to whether or not they should be classified as the legally recognised category 'mutagenesis', which is exempted under the EU GMO legislation.[16] In 2018 the Court of Justice of the European Union ruled that techniques of site-directed mutagenesis, or gene editing, do not fall within this exemption.[17] However, the Advocate-General, a permanent adviser to the Court who prepares an authoritative opinion before the Court comes to a decision, considered that techniques of site-directed mutagenesis should fall under the mutagenesis exemption.[18] This important difference in interpretation could arise because the GMO legislation itself did not provide a clear answer on the legal status of these new technologies.[19]

The Court's ruling provided clarity on the legal status of site-directed mutagenesis, but the GMO legislation that was declared to be applicable to these techniques was considered by many

[11] See Ducuing, 2022, who also argues that the innovation principle should not have the same weight as the precautionary principle.
[12] With thanks to Prof. Evert Stamhuis fort his addition. See also Bennett Moses, 2013, p. 18.
[13] Supreme Court of the Netherlands 20 December 2019, ECLI:NL:HR:2019:2006 (Urgenda); International Court of Justice 12 November 2024, ECLI:NL:GHDHA:2024:2099.
[14] Although, as evidenced by the cited climate case, there is a tendency to make more proactive use of the traditionally reactive civil liability law. See De Jong (2016) for a legal defence of this tendency. However, success is not guaranteed, as demonstrated by the overturning on appeal of the CO_2 reduction order imposed on Shell by the court.
[15] This is in line with the observation by Bennett Moses (2013, p. 7) that the term 'regulatory disconnection' has added value because 'it allows one to observe disconnection even where there is no "legal" disconnection'.
[16] See Directive 2001/18/EC, Art. 3(1) and Annex 1B.
[17] CJEU 25 July 2018, C-528/16, ECLI:EU:C:2018:583 *(Confederation paysanne and Others v Premier ministre and Ministre de l'agriculture, de l'agroalimentaire et de la forêt)*.
[18] Opinion of Advocate General Bobek 18 January 2018, C-528/16, ECLI:EU:C:2018:20.
[19] See Bergmans et al., 2020.

scientists and EU member states to be too restrictive, for one thing because political obstruction had for many years made obtaining authorisation for placing on the market of GMOs under this legislation almost impossible.[20] The applicability of these rules severely hampers innovation based on site-directed mutagenesis techniques, which are seen as highly promising. In fact, scientists consider site-directed mutagenesis to be much more precise and safer than 'conventional' genetic modification *and* conventional mutagenesis.[21] From this perspective, the application of the GMO legislation to products of site-directed mutagenesis on a case-by-case basis can be seen as an example of over-inclusive regulation which obstructs both innovation and safety. The initial legal uncertainty has therefore been supplanted by a continuation of regulatory disconnect in a new form. The EU legislative proposal for new genomic techniques (NGT),[22] published in 2023, which includes site-directed mutagenesis techniques, should be understood as an attempt to address this disconnect.

Grey areas cannot be properly understood by focusing only on the difference in pace and the disconnection between technological change and evolution of the regulatory framework. Addressing the problem of grey areas requires more than factoring the latest scientific and technological developments into the regulatory framework and striking the right balance between safety and innovation. The regulation of technology also involves ethical, societal and political considerations, and these cannot always be kept in separate boxes. For example, consideration of risks may involve hidden ethical or political arguments, especially when risk is the only valid argument from a legal point of view, which is largely the case in the GMO legislation.[23] These types of considerations, and shifts in positions taken, have an effect on the regulatory framework or how it is applied, and therefore also on the emergence or the response to grey areas.

In addition, the various actors involved have different opinions, for example on which ethical standards should be used and what the right balance is between safety and innovation. What one EU member state considers to be a desirable innovation, for example, may be considered to be a retrograde step by another. This means that there may different opinions on the definition of a grey area and on whether this is actually a problem that needs to be fixed. The governments of some EU member states, and certainly a part of the organic sector, feel that it is right that products of site-directed mutagenesis fall under the GMO legislation.[24] They are unlikely to agree with the conclusion in Box 2.1 that there is a problem of over-inclusive regulation and regulatory disconnect.

Lastly, the way in which regulation, scientific knowledge and technological development have been written about should be problematised. The regulatory framework is seldom entirely clear cut, but is the subject of a discourse in which different interpretations compete for precedence. In practice, there can be different opinions on how much of a grey area there actually is and how far creative interpretations of the rules can provide a solution. Of course, the interpretations of authoritative actors, such as regulatory agencies and the courts, carry more weight because

[20] See e.g. Mampuys, 2021.
[21] See e.g. Van der Berg et al., 2021.
[22] Proposal for a Regulation of the European Parliament and of the Council on plants obtained by certain new genomic techniques and their food and feed, and amending Regulation (EU) 2017/625 (COM(2023) 411 final).
[23] See inter alia Trump et al., 2023; COGEM, 2014.
[24] See e.g. MacNaghten & Habets, 2020.

they have the power to have the last word on competing interpretations. While that provides a practical solution, it does little to resolve the fundamental ambiguity of most legal rules.[25] That is another reason why the question of grey areas – situations in which the rules are insufficiently compatible with the latest technology – is not a purely factual one. Answering it requires legal interpretation, and this inevitable involves the possibility of multiple interpretations.

Moreover, unequivocal use of the terms 'scientific knowledge' and 'technological developments' does not do justice to reality. Discussion is inherent in scientific discourse, in the same way that legal rules are subject to differences in interpretation. Debate is a means to advance science, which is why science should ideally be open, provisional and undetermined. These characteristics of 'ordinary science', as Jasanoff calls it, are of little use when scientific knowledge has to be put to use in making and interpreting the regulatory framework, an exercise that Jasanoff refers to as 'regulatory science'.[26] The scientific and technological domain is characterised by uncertainty, impermanence and debate, collectively referred to as scientific and technological grey areas by Bonnin Roca,[27] and these cannot easily be incorporated into legal rules. Where some of this does find its way into the regulatory framework, it can lead to legal uncertainty or legal grey areas. But regulators generally want to provide clarity to innovators and the public, at least for a certain period of time. To do so, they have to make decisions and quantify the unquantifiable. This conversion of science and technology data into clear information and decision means that rules can never fully reflect the scientific and technological state of the art, in which uncertainty and debate are never absent. This means that by definition there is a fundamental and indissoluble regulatory disconnection, even when the regulator does everything possible to keep abreast of developments.

2.2 Robust regulation

Although regulation-to-technology disconnection can never be completely avoided, the theory behind this concept assumes that the aim should be to achieve the best possible connection between regulation and technology. However, the changeable nature of science and technology means that this connection cannot be static. Keeping a disconnect as limited and short-lived as possible therefore requires continual **regulatory reconnection**.[28] Regulation that is dynamic enough to meet this challenge is referred to by Du & Heldeweg as 'resilient'.[29]

A crucial feature of 'resilient' regulation is the ability to adapt to changing conditions, with a specific focus on adapting to scientific and technological developments.[30] This emphasis on adaptability, or related terms such as adaptivity and flexibility, is central to definitions of resilience outside the domain of regulation. In physics, resilience refers to the ability to return to the previous state after something has been compressed or stretched.[31] Another definition of

[25] Hart, 1961; Tamanaha, 1997, p. 196–203.
[26] Jasanoff, 2005, p. 108.
[27] Bonnin Roca, 2024, p. 5.
[28] Brownsword, 2008, Chapter 6.
[29] Du & Heldeweg, 2018, p. 293. Robust regulation requires a number of additional conditions, discussed later in the text.
[30] Not without reason is there a great deal of literature on concepts such as 'adaptive regulation' and 'adaptive governance', which are also used in this section. See e.g. Blais & Wagner, 2008; Brass & Sowell, 2021; Greer & Trump, 2019.
[31] Cf. Anholt, 2021, p. 23–25.

resilience is suppleness and agility. Applied to people, resilience refers to the power of both body and mind to recover quickly. People show resilience when they recover from setbacks such as illness, stress or loss, or when they pick up the pieces in unusual situations such as during or after war or natural disasters.[32] Nature is also said to be resilient when it adapts as far as possible to changing environmental conditions or recovers after natural disasters.[33] In relation to humans or nature, resilience means something different from the ability to bounce back. Recovery following adversity seldom means returning to the same situation, but achieving a new equilibrium in which the traces of impactful events are still recognisable, even after recovery. That resilience in this context involves changes over time becomes clearer in the second meaning of resilience, which refers to the capacity to adapt to changing circumstances.[34]

However, the concept of resilience encompasses more than just adaptability. Resilience also implies strength and stability; in other words, robustness.[35] This puts the adaptability element in context and limits it. Adaptability is not a goal in itself, but a means to achieve other goals. Adaptability serves stability and strength. Resilience is not the same as always going with the flow and running the risk of becoming the plaything of circumstance, but adapting where necessary and maintaining course as much as possible.

This notion of resilience, in which adaptability is not a goal in itself but a necessary attribute of maintaining a stable course towards one's own objectives, is also reflected in the brief definition of 'robust regulation' formulated by COGEM in the call for this study: 'Regulation must be robust enough to keep pace with new developments, while ensuring safety and not unnecessarily obstructing innovation.' Ensuring safety without unnecessarily obstructing innovation is in fact a reformulation of the goal of biotechnology regulation, with the possibility of moving with events as a means towards that goal.

In this context, attention must be given to the potential tensions between the adaptive character of robust regulation and the legal robustness which this and all other forms of regulation must meet. Legal robustness is the degree to which the legislation and regulations can withstand legal challenges by stakeholders.[36] It is precisely those types of laws and regulations with a strong adaptive character, such as temporary legislation and regulatory sandboxes,[37] that can be vulnerable in the face of constitutional principles such as legality, legal certainty, legal equality and proportionality.[38] Take, for example, the principle of legal certainty.[39] One risk of easily adaptable regulations is that the rules become less predictable, which can ultimately impair the twin goals of protection and innovation, and can lead to legal proceedings that threaten the durability of the regulatory framework.[40] The conclusion that can

[32] Cf. e.g. Fekkes, De Wolff & Rutgers, 2023; Anholt, 2021, p. 23, 25–26.
[33] Anholt, 2021, p. 28–30.
[34] Cf. Anholt, 2021, p. 30.
[35] Cf. Anholt, 2021, p. 27.
[36] Philipsen, Stamhuis & De Jong (2021), who draw attention to this tension, use the term 'legal resilience'.
[37] See § 3.3.1 and § 3.5.2.
[38] Philipsen, Stamhuis & De Jong, 2021; Du & Heldeweg, 2018; Le Blansch et al., 2022.
[39] Du & Heldeweg (2018, p. 296) characterise this as follows: 'Legal certainty enables citizens to predict rights and duties and to be protected against sudden changes, and provides a favourable legal environment for enterprises to make decisions to invest.'
[40] Philipsen, Stamhuis & De Jong, 2021, p. 1135–1136; Du & Heldeweg, 2018, p. 295–297; Nielson, 2018.

be drawn from this is that the challenge of robust regulation is to reconcile adaptivity with legal robustness.[41]

The above reasoning leads to the following definition: **In this report robust regulation means regulation that can address technological and scientific developments in a timely and legally robust manner in order to protect public interests and promote (or at least not unnecessarily hamper) innovation**. The tensions that can arise between the public interests to be protected, such as safety and consumer choice, and the promotion of innovation are taken into account in this report. In this report the term 'regulation' as used in this definition is interpreted in a broad sense: in addition to national and EU legislation, it also includes regulation by regulatory government agencies, as well as rules set down in the case law and 'soft law'.[42]

In a 2022 research report commissioned by COGEM, Le Blansch and others also used the term *veerkracht* (resilience) in the context of biotechnology.[43] The report was prompted by the Covid pandemic and focused on resilient policy in unexpected circumstances leading to a temporary state of emergency. In the present study, our main concern is not unexpected circumstances, but rather robust regulation for scientific and technological developments in 'normal' circumstances.

2.3 An interactive view of robust regulation

As mentioned in § 2.1, grey areas are not all about a disconnect between the regulatory framework and technology, but also other factors that play a role in the emergence and approach to resolving grey areas, such as ethical, societal and political considerations. These are also included in our understanding of robust regulation. Strictly speaking, the definition presented in § 2.2, which is based on regulation-to-technology-connect, can be expanded by recognising the significance of regulation-to-society-connect, regulation-to-politics-connect, regulation-to-ethics-connect, etc. To reduce the complexity of the concept, we do not go so far as to explicitly include these aspects in the definition of robust regulation, but choose to focus primarily on the relationship between regulation and technology. However, we take full account of the importance of the political, societal, economic and ethical context within which the problem of the 'regulation-to-technology-(dis)connection' plays out.[44] This perspective is consistent with an interactive approach to regulation. We explain this in more detail below.

Regulations are often explained in terms of their normative, constitutional and instrumental functions. The normative function of regulations concerns behavioural standards laid down in laws and rules. The constitutional function refers to the organisation and constitutional basis of the State, with an important part played by the rules for the structure of the State and fundamental rights. The instrumental function of regulations is to ensure that the public comply

[41] Cf. EESC, 2016, in which the combination of adaptivity and legal clarity and certainty are mentioned as characteristics of 'future-proof legislation'.
[42] See inter alia Bennett Moses, 2013, p. 4; Andone & Coman-Kund, 2022.
[43] Le Blansch et al., 2022.
[44] Cf. inter alia Faulkner & Poort, 2017; Trump et al., 2023.

with standards or behave in an appropriate way. This means that regulations are instruments of governance,[45] with penalties, subsidies, fines, permits, etc. used as steering mechanisms.

Beyond these classical functions of regulation, legal philosophy also identifies an **interactive or reflexive view of regulation**.[46] According to an interactive view, laws and regulations can also have a **communicative or symbolic function**, in which legal standards provide a framework for further communication.[47] In this approach, laws and rules are not seen as marking the end of the debate or as a solution to the whole problem, but the development of legal standards and frameworks is seen as an ongoing process which interacts with technological and societal developments. Legal standards are not set in stone, but are open and aspirational in nature. The standards are further developed through interaction with practice. This does not mean that anything goes; these open, aspirational standards provide direction and structure for the further development of standards.[48] This does justice both to the dynamic nature of technology and to political and public debate.

2.3.1 Regulatory knowledge

An interactive approach to regulation provides several insights of use for this study. First, this approach provides fertile ground for Faulkner and Poort's insight that choices for a particular type of technology regulation are based on different types of knowledge. Besides technological knowledge, they identify other knowledge domains relevant to technology regulation, such as legal knowledge, social knowledge, ethical knowledge and economic knowledge, with an emphasis on the first two domains.[49] By legal knowledge, Faulkner and Poort primarily mean the influence a specific legal context has on the choice of a particular form of regulation. Not every option is available in every legal context. The legal system, the legal culture, legal principles, legal authorities and legal decisions made in the past, and the path dependencies they created, make certain regulation options more obvious choices and others less suitable or even impossible. Faulkner and Poort interpret social knowledge in a broad sense to include not only 'hard' social and economic facts, but also social attitudes towards and moral concerns regarding technological developments. Faulkner and Poort refer to all knowledge domains relevant to technological regulation as 'regulatory knowledge'.

In 2004, Poort and Quintavalla added a further type of knowledge to this framework: sustainability knowledge.[50] They showed that knowledge about sustainability does not fall within any of the other knowledge domains. Sustainability knowledge concerns the technological possibilities for achieving sustainability objectives; it refers to the differing social views on what a sustainable future should look like, to the economic feasibility of sustainability objectives, the policy strategies for attaining them and to sustainability as a legal principle.[51]

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[45] Glastra van Loon, 1988. There are also other ways to classify law, but this is the most common distinction.
[46] Witteveen, 2005; Van Klink & Witteveen, 1999.
[47] Poort, 2013, Chapter 3; Poort, 2016.
[48] Poort, 2013, Chapter 3.
[49] Faulkner & Poort, 2017, p. 212–213.
[50] Poort & Quintavalla, 2024.
[51] Idem.

The theoretical framework of regulatory knowledge concerns the knowledge needed to draw up a regulatory regime for technology within a certain context. For this study, however, it is also a tool for analysing which knowledge domains have an influence on the complexity of a grey area in a specific case and what this means for the form that robust regulation could take in that case. This is explained in more detail in Chapter 4.

2.3.2 Stakeholder involvement

The second insight provided by the interactive approach is that the various types of knowledge relevant to technology regulation should be given a voice by involving a wide variety of stakeholders in the development of the regulations. These stakeholders should not only be involved in technological innovation, but must also include 'lay people' representing a diversity of views and experiences in society. The literature contains numerous arguments for such stakeholder involvement under various headings and expressed in different ways.[52] Here we limit ourselves to discussing a proposal by Poort et al. (2022) for structured phases of stakeholder involvement.

Poort et al. explain this approach from a deliberative and a political dimension.[53] In the first track (the deliberative dimension) the problem is investigated and structured (step 1). In this process, the various layers of the problem are uncovered with the aim of identifying and recognising the diversity of views and the importance of facts.[54] In the second track (the political dimension) the problem is defined (step 2) and decisions taken (step 3).[55] Although steps 2 and 3 both belong to the political dimension, from the perspective of stakeholder involvement they are two distinct steps. This is because defining a problem requires a different conceptual framework than making a decision, although both have a political dimension because decisions have to be made in both steps – even if not all parties involved agree on the problem definition and the chosen solution.

In this study, we based the structuring of the case studies in Part II on this division into two tracks. We analysed the case studies in two steps: 1) problem analysis and 2) solution strategies. The aim of the case studies was to analyse the grey areas and problem areas in the legal framework (problem analysis) and to explore possible solutions for addressing these grey areas better in the future (solution strategies). When exploring solution strategies, our aim was to find ways of making the legal framework more robust. For the analysis of the grey areas and the problem areas in the legal framework, we took the deliberative track, exploring and analysing the various layers of the problem and diversity of views. We approached the identification and evaluation of solution strategies from the political dimension, which is required for a proper analysis of the feasibility of solution strategies. Besides legal feasibility, the political willingness to develop solutions and integrate them into the legal framework was also investigated. This is explained in more detail in Chapter 4.

[52] See e.g. Bonnin Roca, 2024, p. 2; Mourby et al., 2022; Trump et al., 2023.
[53] Poort et al., 2022.
[54] Idem, p. 1212.
[55] Idem, p. 1213.

2.3.3 Political will

The third insight we obtained from the interactive approach is that meaningful consideration of robust regulation is only possible once its fundamentally political nature is recognised. Political actors are almost always involved in the development and amendment of regulations. Even when that is not the case, weighing up the information from different knowledge domains relevant to regulating a technology and choosing a solution based on the outcome are essentially political acts because a balance has to be found between conflicting values, interests and views. This is reflected in steps 2 and 3 of the stakeholder involvement approach described in § 2.3.2. In practice, attempts are made to depoliticise these decision-making processes, for example by limiting the types of knowledge that may be considered and/or delegating important decisions to parties without a democratic mandate, such as regulatory agencies and the courts. However, depoliticisation and technocracy cannot permanently suppress or eliminate the political element. Political debate and conflict, which are also related to public debate and conflict, will remain and may emerge elsewhere in less desirable forms, such as political obstruction of GMO authorisations in EU committee procedures, where there is no formal place for political argument.[56] Against this background, Mampuys (2021) and Poort et al. (2022), inspired by an interactive view of regulation, argue for repoliticising decision-making and public debate about the GMO legislation.

Recognition of the inherently political dimension of regulation implies an important disclaimer to the discussion of building blocks for robust regulation in Chapter 3. There are virtually no conceivable legal solutions to grey areas outside the political sphere, at least none that could last. And it is also highly doubtful whether that would be desirable. This means that any way of creating a more robust regulatory regime will depend to a great extent on political will. Without it, it may be possible to design an exemplary robust regulatory system on paper, but it would have no chance of working. In Chapter 3, where relevant, we will explicitly discuss the political feasibility of certain solutions.

[56] See inter alia Kortleven, 2013, Chapter 5; Mampuys, 2021.

3 Building blocks for robust regulation

3.1 Stretch or break

In the article by Faulkner and Poort cited in § 2.3.1, the authors identify two regulatory strategies used in practice when new scientific or technological developments threaten to cause a regulation-to-technology disconnect: **stretching** and **breaking**.[57] The first strategy involves keeping the existing regulations, but interpreting the legal definitions in ways that stretch or expand their scope in order to accommodate new developments. The second strategy comes into play when the stretching strategy is considered to be impractical or undesirable and involves revising or replacing the existing regulations. The choice of strategy is informed by arguments from the various knowledge domains defined by Faulkner and Poort as regulatory knowledge.

It is important to realise that certain arguments (for example, about the design of the existing legal system, or the characteristics of certain technological applications, or strong public resistance to such applications) may lean heavily towards one of these two strategies, but that the choice is never a completely objective one. While arguments from multiple knowledge domains (legal, technological, social, ethical, economic) are weighed up, a complete consensus can never be reached on the outcome of an appraisal of heterogenous arguments – all the more because within each of these knowledge domains there are different perspectives on natural or social reality, differences in interpretation and/or value conflicts, as discussed in § 2.1. In a given situation, therefore, the choice between stretching or revising the existing regulations can never be a categorical one made from 'Archimedean point'.

In this chapter the adaptive strategies of *stretching* and *breaking* are considered to be the basic templates for all attempts to make the regulatory framework more robust. The building blocks for more robust regulation examined in this chapter take one of these strategies as their starting point: they either focus on increasing the 'stretching capacity' of the rules or they attempt to make the rules easier and quicker to amend. Sometimes the two strategies are combined, which means that the analytical distinction between stretching and breaking is not absolute.

The following sections, which are based on a literature study, discuss various building blocks which could be used for the development of a more robust regulatory regime according to the definition of robust regulation in § 2.2. These building blocks can be divided into four categories: more abstract formulation of legislation (§ 3.2), temporary and experimental legislation (§ 3.3), judicial law-making (§ 3.4) and regulation by regulatory agencies (§ 3.5). Each of these building blocks from the literature is evaluated in the light of the question 'To what extent can this solution contribute towards a regulatory regime that can address technological and scientific developments in a timely and legally robust manner to ensure public and environmental safety while promoting (or at least not unnecessarily hampering) innovation?'

3.2 More abstract formulation of legislation

In the literature, increasing the 'stretching capacity' of regulations is discussed under a number of headings. The common denominator is a tendency to make rules more general. Formulating rules in more abstract wording increases the likelihood that they will be able to accommodate

[57] Faulkner & Poort, 2017.

future developments. It is precisely the specific references in regulations, the factual details, techniques and conditions applying at the time they were drawn up, that are usually the first to become outdated.

3.2.1 Standards, goal-based regulations and reduction of technology specificity

The first heading under which such generally formulated rules are discussed in the literature is that of **standards**. According to McGinnis and Wasick, standards differ from 'normal' legal rules in their 'open-endedness', which leaves more leeway to accommodate changing facts. This makes them more suitable for more complex and changeable situations.[58] The downside of the fact that standards are less specific than rules is that it is less easy to interpret and apply them in a given situation, and this leaves more room for discussion. Whereas formulating a specific rule requires much work and discussion in advance, standards require relatively more work and discussion in their application once they have been adopted.[59] At the same time, the distinction between standards and rules is an ideal one; in practice the two categories overlap and it is not possible to draw a clear line between them.[60]

An obvious question is what information should standards contain to provide guidance, as complete open-endedness would render them meaningless. One possible answer could be open standards such as those found in the Dutch Civil Code: 'reasonableness and fairness' (Article 6:248), 'unlawful act', 'violation of someone else's right' (Article 6:162). McGinnis & Wasick give the example of a speed limit: a specific rule would prescribe a maximum speed, such as 100 km/h, while a standard could require a motorist to drive at a 'reasonable speed',[61] in which what constitutes a 'reasonable speed' can vary according to the situation.

In such open standards, rules are stripped down to the objectives to be achieved and/or the interests or values to be protected.[62] Regulations that are so generalised that objectives, interests or values are described but no detailed prescriptions are given on the means to implement them are referred to in the literature as **goal-based regulation**,[63] **principles-based regulation**[64] and **open-texture** rules.[65] These concepts overlap with the concept of standards, but differ in some respects. Here we can also recognise the interactive approach to law and its communicative function as described in § 2.3. The use of open, aspirational standards helps to facilitate and give direction to the further development of standards in interaction with practice.[66]

By not mentioning specific means for achieving the stated objectives, goal-based regulation is in principle better able to accommodate future developments than regulations that focus on the means. It is reasonable to assume that the objectives of technology regulation will remain relatively stable over a longer period of time. However, there will always be technological

[58] McGinnis & Wasick, 2014, p. 993.
[59] Idem, p. 1027–1028.
[60] Idem, p. 1027.
[61] McGinnis & Wasick, 2014, p. 1027.
[62] Idem, p. 1027.
[63] Westerman, 2014, p. 125; Stoter & Stout, 2010.
[64] Westerman, 2014, p. 125; Black, 2008.
[65] Du & Heldeweg, 2018, p. 293–294.
[66] See § 2.3.

advances, with associated risks, that put these objectives to the test, and new ways will always be needed to deal with those risks. Goal-based regulation is less likely to become obsolete because it avoids the use of rules such as 'Do not use chemical X, as it is known that this may cause health hazard Y' in favour of rules of the type 'Do not perform any action that may incur health hazard Y.'[67]

Goal-based regulation for technologies can therefore take a form that approaches **technological neutrality**,[68] or, more correctly, a **reduction of technological specificity.**[69] Bennett Moses observes that if we begin with the question of how to protect society against the risks of technology X, the result will probably be regulations geared to the risks of that technology. According to her, this is the way of least resistance. 'Regulators do not need to worry *generally* about how to frame new laws in a way that will manage particular risks or protect particular values if they are asked only to think about how a particular technology should be regulated.'[70] She says that despite the specific features of new technological possibilities, there are many similarities between the problems raised by past, current and probably future technologies.[71]

Bennet Moses illustrates this with the example of nanotechnology. The risks associated with this technology are closely related to the risks of other chemical substances: 'They are different at the level of specifics … but they are not different in kind.' She concludes that there was no need for specific regimes for nanotechnology and that application of more general regulations for chemicals would have been enough, as long as they were adapted to incorporate the latest knowledge resulting from the development of nanotechnology. More generally, she suggests that some of the regulation problems arising from the development of new technologies are down to the existing regulatory regimes being too technology-specific.[72]

To address the problem of outdated regulations, Bennett Moses argues that technology itself should not determine our thinking. She proposes starting from the values to be protected, in the knowledge that these values can be threatened not only by various technologies, but also by non-technological developments. Taking a technology-neutral perspective, we should then determine whether regulation is needed to protect these values, and if so, what type of regulation.[73] The provisions in any resulting regulations should be formulated in such abstract terms that they can be applied to future threats to those values, but at the same time they must be concrete enough to make them workable in practice.[74] This argument is compatible with the idea behind goal-based regulation in general.

In her argument against technology-specific regulation, Bennett Moses makes an exception for problems specifically related to a certain technology, for example if there are moral objections

[67] These examples of rules are taken from Du & Heldeweg, 2018, p. 293.
[68] Cf. Bennett Moses, 2007, p. 276; Bennett Moses, 2013, p. 14–19; Du & Heldeweg, 2018, p. 294.
[69] Complete technological neutrality will prove to be difficult and/or undesirable to achieve in practice. See Puhakainen & Väyrynen, 2021, p. 8.
[70] Bennett Moses, 2013, p. 15.
[71] Idem, p. 16.
[72] Idem, p. 15–16.
[73] Idem, p. 17, 19.
[74] Cf. Bennett Moses, 2007, p. 276.

to it.[75] Examples include genetic modification of animals and genetic modification of plants that involves gene transfer between species (transgenesis).[76] Regardless of the safety risks that may be involved, Bennett Moses thinks that in such cases critics are entitled to argue for a separate regime.[77]

3.2.2 Reservations concerning the abstract formulation of legislation

While the major advantage of formulating legislation in more general terms is the 'stretching' of rules to make them better able to accommodate future changes, it also has significant disadvantages. Aiming for technological neutrality in regulations may not turn out to be so useful in practice. The uncertainties inherent in a new technology can make it difficult to determine whether or not a technology-neutral regulation would be a suitable option.[78] Moreover, by their very nature, regulations formulated in general terms provide less guidance and therefore less legal certainty.[79] This is a significant disadvantage from the protection and innovation perspective.[80] In terms of our definition of robust regulation, the advantage of addressing new developments quickly is at odds with the legal robustness of taking this route.

At the same time, when legislation is formulated in abstract terms, it is assumed that the meaning will be interpreted and clarified by the decisions and actions of the courts, regulatory agencies and private parties.[81] Judges make more specific rules by applying standards and goal-based regulations to concrete situations; regulatory agencies translate abstract rules into more specific rules and then apply them to concrete situations; private parties draw up protocols to which they commit themselves and/or others. These actions gradually reduce the uncertainty inherent the abstract formulation of legislation, but the degree of uncertainty will generally remain higher than when specific rules are made at the legislative level. This has to do with the decentralised and gradual nature of the interpretation of abstract rules by the courts, regulatory agencies and private parties, who, in the spirit of the regulations themselves, take different approaches to complying with the rules.[82] This means that information on the specific interpretation of an abstract rule is diffuse, being made in different places and at different times, making it more difficult and costly to collect than for a more specific rule.[83]

Not only legal certainty, but also the flexibility of abstract legislation depends to a large extent on the specific interpretation given to it by the courts, regulatory agencies and other actors. These specific rules have to be amended or replaced on a regular basis as new developments arise. The stretchability of abstract legislation therefore relies on the fact that the resulting specific rules in lower-level regulations can be 'broken' more quickly and easily, making stretchability heavily dependent on the capacity and willingness of these lower tiers of authority to regularly update the specific interpretation of abstract rules. We look at this in more detail in § 3.4 and § 3.5.

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[75] Idem, p. 15.
[76] See e.g. Poort, 2013; Kortleven, 2013, p. 238.
[77] Bennett Moses, 2013, p. 15.
[78] Puhakainen & Väyrynen, 2021, p. 7.
[79] McGinnis & Wasick, 2014, p. 1030; Puhakainen & Väyrynen, 2021, p. 6.
[80] Cf. Du & Heldeweg, 2018, p. 296.
[81] Bennett Moses, 2007, p. 277–278; McGinnis & Wasick, 2014; Westerman, 2014.
[82] Cf. Kołacz, Quintavalla & Yalnazov, 2019, p. 8; McGinnis & Wasick, 2014, p. 1027–1028.
[83] McGinnis & Wasick, 2014, p. 1029–1030; Puhakainen & Väyrynen, 2021, p. 8; Cappelletti, 1981, p. 47.

Lastly, there may be reservations regarding the constitutional and democratic legitimacy of abstractly formulated legislation. If abstract standards, objectives, aspirational norms or values are defined at the legislative level and their interpretation left to other actors, the legislature, which has the constitutional and democratic mandate for regulation, will be largely stripped of its regulatory power.[84] Moreover, this also means that much of the content of the regulations will not be subject to oversight by representative bodies.[85] The idea that goal-based regulation takes a different approach to meeting the demands of democratic involvement and oversight, namely by giving the relevant stakeholders a role in the interpretation of the regulations and through accountability mechanisms for implementing goal-based rules, is criticised by Westerman. She points out, for example, that stakeholder involvement is not always voluntary[86] and that accountability is not to the public but to the government.[87]

3.2.3 Dynamic regulation

In the literature, a form of regulation is discussed that is designed to accommodate different situations in the future, but is not formulated in such abstract terms that its applicability depends on specific lower-level regulations. This is called dynamic regulation. McGinnis and Wasick define **dynamic rules** as 'rules that automatically change without intervention by the rule giver according to changes in future conditions that the rule itself comprehensively and accurately fixes.'[88] At first sight, these characteristics of dynamic rules would seem to combine the best of both worlds: future-proofing and clarity. This is achieved by incorporating the uncertainty of future facts as a variable in a dynamic rule, thereby allowing it to keep up with future facts while providing certainty on the limits that will apply as these facts emerge. McGinnis and Wasick give the example of the debate on climate change, which, besides the disagreement on principles and values, is fuelled by debate about empirical facts. This debate about facts does not have to prevent regulation if the rules are formulated in a such a way that their implementation depends on empirical information, such as on temperature changes, that will become available over the next five to ten years.[89]

However, the disadvantage of dynamic rules is that they are not capable of accommodating all possible uncertain situations. This is the downside of their biggest advantage, their rather mechanical functioning.[90] To make these rules work without the need for intervention, the incorporated uncertainty has to be so narrowly defined that it works only for the 'known unknowns'. 'Unknown unknowns', such as the new technologies that will emerge in ten-years' time and what they mean for current regulations, cannot be captured in precisely defined dynamic rules. This limits the degree to which dynamic regulation can be future-proof.

[84] Bennett Moses, 2007, p. 278.
[85] Westerman, 2014, p. 129, 134.
[86] For example, private parties can be required to develop protocols to interpret a certain statutory standard.
[87] Westerman, 2014, p. 130–134.
[88] McGinnis & Wasick, 2014, p. 1039.
[89] Idem, p. 1039–1043.
[90] Idem, p. 1046.

3.3 Temporary and experimental legislation

The intermediary step of dynamic regulation, which explicitly incorporates change into the rules without altering the formulation of the regulations themselves, brings us closer to solution strategies that build on the 'breaking' strategy: increasing the robustness of regulations by making them quicker and easier to amend. One way to achieve that at the legislative level is through the use of temporary legislation with or without an experimental objective. This type of legislation contains provisions that provide for its temporary nature. **Compared to 'ordinary' legislation, temporary legislation turns the standard rule of continuity on its ahead**. Ordinary laws remain in force until they are terminated or amended by new legislation (or sometimes by a judicial decision). Temporary laws or temporary clauses in laws expire on a certain date or when a certain condition is met, the 'horizon' in **horizon provisions** or **horizon legislation**, unless legislative action is taken to renew them.[91]

3.3.1 The promise of temporary and experimental legislation

Temporary legislation can be divided into legislation with and without explicit experimental objectives. **Temporary laws with an experimental objective aim to test potential solutions for a limited period and or on a limited scale** to determine whether or not they should be applied permanently on a wider scale. This implies that information has to be collected to decide about the follow-up to the experimental measure, which is why in the literature **learning and evaluation mechanisms** are considered to be a determining feature of experimental legislation.[92] Temporary legislation without an experimental objective is used in crisis situations or for situations that are considered to be of a temporary nature.[93] In practice, it is sometimes difficult to distinguish experimental legislation from non-experimental temporary legislation. For example, laws with an explicitly experimental objectives do not always contain evaluation mechanisms.[94] At the same time, temporary laws without an explicitly experimental objective are sometimes considered to be disguised experimental laws,[95] and the fact that a temporary law does not contain any evaluation provisions does not necessarily mean that no policy or legislative lessons can be learned.[96]

Du & Heldeweg distinguish between three types of experimental legislation, each of which has a 'normal' counterpart. The first is an experimental form of **derogation**, in which a temporary exemption is made from an existing regulatory regime, for example for a certain category of actors or certain technological applications, to test if it is preferable to relax the existing regime, either in whole or in part.[97] An example of such a derogation, but without an explicit experimental objective, is Regulation (EU) 2010/1043, which suspended the necessity of conducting an environmental risk assessment of clinical trials with GMOs for the development of Covid-19 vaccines or medicines for the duration of the pandemic.[98]

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[91] Bar-Siman-Tov, 2018; Gersen, 2007; Ranchordás, 2015.
[92] Bar-Siman-Tov, 2018; Ranchordás, 2015; Van Gestel & Van Dijck, 2011; Du & Heldeweg, 2018, p. 291–292.
[93] Cf. Bar-Siman-Tov, 2018.
[94] Bar-Siman-Tov 2018, p. 207.
[95] Ranchordás, 2013, p. 231.
[96] Cf. Poort & Kortleven, 2021.
[97] Du & Heldeweg, p. 292, 294.
[98] Despite the absence of an explicit experimental objective, it can be said that this derogation had a latent experimental function; see Poort & Kortleven, 2021, p. 12–13.

The second type is an experimental form of **devolution**, giving decentralised authorities the option of pursuing a different regulatory regime. The resulting information is then evaluated centrally or collectively to determine in what form the overarching regulatory regime should be taken forward.[99] Devolution from the national to the regional or local level, or from the EU to its member states. An example of devolution with an experimental objective is Article 23(1) of GMO Directive 2001/18/EC, which permits member states to temporarily prohibit the use and/or sale of a previously authorised GMO in their territory on the basis of new information about the potential risks involved. The European Commission and the other member states must immediately be informed of any such prohibition and the underlying risk information, after which a decision on its validity is made at the EU level.

In practice, the option of temporarily prohibiting GMOs on grounds of risk was used improperly,[100] which eventually led to the introducing the possibility of imposing a permanent national prohibition on the cultivation of GMOs on social and economic grounds.[101] In the classification by Du & Hildeweg, the option of a national prohibition on cultivation is an example of the normal devolution variant. The purpose of normal devolution is not to 'test' existing regulations, but to permit political autonomy.[102] The possibility of prohibiting GMOs was first introduced in the form of experimental devolution (temporary on grounds of risk) and when that proved unsuccessful the option of prohibiting GMOs via normal devolution (permanent on social and economic grounds) was introduced.

The third type of experimental regulation is an experimental variant of 'open-texture' rules.[103] Experimental open texture is a temporary strategy to encourage alternative practices under a particular standard or norm, with the aim of gathering information for evaluation and decision-making on a permanent approach to regulation at a later date. Du & Heldeweg call this 'learning by interpretive variance'.[104]

Compared with ordinary legislation, temporary and experimental laws are seen as a means to ensure that legislation keeps pace with technological and societal changes because they can generate useful information, bridge the period needed to gather information and facilitate and speed up the adaptation of existing legislation.[105] As Ranchordás stresses, temporary and experimental legislation can help to create an innovation friendly environment. Temporary instruments, such as sunset clauses, are useful for keeping legislation more in step with the lifecycles of innovations and can reduce the regulatory burden by shortening time-consuming procedures and simplifying the repeal of outdated rules.[106] Conversely, temporary and experimental laws can also be helpful in imposing timely restrictions on innovations that would probably have negative consequences. The uncertainty paradox inherent in taking early

[99] Du & Heldeweg, p. 293–294.
[100] Kortleven, 2013, p. 273, 276–278, 307–311.
[101] See Directive (EU) 2015/412; Mampuys & Poort, 2019.
[102] Du & Heldeweg, 2018, p. 294.
[103] Du & Heldeweg, 2018, p. 293–294. See § 3.2.1 on 'normal' open texture rules.
[104] Idem, p. 293.
[105] Gersen, 2007, p. 278; Marchant, 2011, p. 29; Ranchordás, 2013; Ranchordás, 2015.
[106] Ranchordás, 2015, p. 203, 215, 218–219.

regulatory action (action is needed, but too little is known to decide on the right action)[107] can be better addressed with temporary instruments than with conventional legislation.

The establishment of the Committee on Animal Biotechnology (*Commissie Biotechnologie bij Dieren*, CBD) is a good example. The CBD was established in 1997 and given responsibility for considering the ethical issues surrounding the use of animals in biotechnological research.[108] The establishment of this committee and a separate authorisation procedure were justified because, at the time, understanding of these ethical issues was insufficient.[109] After a number of years, it was concluded that a separate ethical review was unnecessary because the ethical objections had become clear. The CBD was therefore no longer needed.[110] From 1 January 2010, biotechnological procedures in animals for biomedical research have been exempt from the ethical review required under the Animals Act.[111] Since no other biotechnological procedures with animals are carried out in the Netherlands, the CBD is no longer active, but has never been formally abolished by law.[112] It may have been clearer and less cumbersome if the CBD had been established under a temporary provision, so that in the absence of a decision to renew its remit it would automatically have expired after a predetermined period of time or fulfilment of a stated condition.

Part of the reason why temporary legislation (either experimental or not) is expected to speed up the legislative response to technological and societal changes is its presumed potential to facilitate the reaching of a **consensus**. In the literature on temporary legislation, it is assumed that achieving a political consensus on a law will be easier (or less challenging) and therefore less time-consuming if the law is temporary rather than valid for an indefinite period.[113] At least two reasons for the assumed link between the temporary nature of legislation and the likelihood of its political acceptability can be distilled from the legislation.

First, the temporary nature of a measure allows political actors to retain control over its future and gives them the option of allowing it to expire after a certain time, also making it possible to postpone coming to a definite decision on the problem in question. This lowers the threshold for supporting a law: despite having doubts or objections, political actors may be more willing to give a measure 'a chance' if it is 'only' temporary.[114]

Second, it is argued that the information generated about the effects of a temporary measure can serve as a fact-based check on the assumptions and intuitions of political actors. Should certain ideas about the functioning of a temporary law prove to be unfounded, political actors would be prepared to revise these ideas in the light of the new information. Conversely, if a measure proves to be ineffective or to have undesirable consequences, it can be more easily revised or repealed. In this way, temporary legislation, especially if it contains provisions for

[107] cf. Bennett Moses, 2013, p. 8.
[108] Art 66(1) *Gezondheids- en welzijnswet voor dieren* (Gwwd).
[109] Art 66 Gwwd; Poort, 2013, Chapter 7.
[110] Poort, 2013, Chapter 7; COGEM 2018.
[111] Rijksoverheid, 2010, *Regelgeving biotechnologie bij dieren is vereenvoudigd* [Newsletter].
[112] COGEM, 2018.
[113] Maltzman & Shipan, 2008; Bar-Siman-Tov, 2018; Gersen, 2007.
[114] Gersen, 2007; Ranchordás, 2015.

evaluation, encourages political actors to acknowledge empirically established findings, thus reducing or bridging ideological divides.[115]

3.3.2 Reservations concerning temporary and experimental legislation

Several observations can be made concerning temporary and experimental legislation. To begin with, the second reason given above for the assumed link between the temporary nature of legislation and the likelihood of its political acceptability seems somewhat naive. The basic assumption appears to be that political and ideological differences of opinion become smaller or less important as uncertainties are reduced and more information becomes available. This may be true to a certain extent, and would appear to depend on the political structure and culture, but it is more likely that ironing out political and ideological differences on the basis of empirical findings will more often than not prove to be difficult. Political actors can simply ignore or downplay unwanted findings or exploit the complexities and ambiguity of the information on the effects of legislation to suit their own views.[116] Such information often allows for different interpretations, especially when dealing with 'wicked problems'. The way in which GMOs are treated in the EU is a good example. Ideological and political differences on GMOs often weigh more heavily than scientific data. Despite the amassed wealth of knowledge about the nature of GMOs and effects of the GMO legislation, the lack of consensus within and between EU member states on the issue of GMO regulation still persists.[117]

A shortcoming of the theory of temporary and experimental legislation is its emphasis on testing the hypothesis behind the legislation. This implies a traditional top-down approach to evaluation that looks mainly at the effects the rules are supposed to have. The blind spot in this approach is the unknowns, and it can easily lead to ignoring bottom-up knowledge about 'why' rules do or do not work. Linked to this, authors writing about experimental legislation do not explicitly acknowledge the need to involve broader societal attitudes to the problem in the evaluation process, but it is just those broader societal attitudes that frustrate the functioning of the legal framework for GMOs in the EU.[118]

Moreover, experimental and temporary legislation is coming under growing scrutiny because it encroaches on fundamental constitutional principles such as legal certainty, legal equality and the protection of legal rights.[119] The fact that experimental legislation can permit differences in the application of rules within the same jurisdiction (national or within the EU) makes this type of legislation vulnerable to the accusation of leading to legal inequality, especially by businesses arguing that competitors who can make use of an experimental regime while they cannot have an unfair advantage,[120] while the temporary and localised exceptions and variety that characterise experimental legislation undermine the clarity of applicable law, and therefore legal certainty. The transient nature of temporary and experimental legislation can also compromise legal certainty. This is especially so for businesses that make use of an

[115] Ranchordás, 2013; Ranchordás, 2015; Van Gestel & Van Dijck, 2011. This line of reasoning is related to the argument by McGinnis & Wasick (2014, p. 1043) in relation to the role dynamic regulation could play in resolving differences of opinion on empirical facts.
[116] Cf. Ranchordás, 2021, p. 3.
[117] See e.g. Mampuys, 2021, Chapter 9.
[118] Poort & Kortleven, 2021.
[119] Philipsen, Stamhuis & De Jong, 2021; Ranchordás, 2021; Du & Heldeweg, 2018.
[120] Philipsen, Stamhuis & De Jong, 2021, p. 1136.

experimental regime and have a clear interest in certainty on the duration of the experiment and what will happen thereafter. They may decide to challenge government decisions taken after the experiment has ended, claiming that the purpose of the experiment raises justified expectations concerning the period after the experiment.[121] That is why the adaptivity achieved by temporary and experimental legislation, like legislation formulated in abstract terms, would appear to be at odds with legal robustness.

Philipsen and others are of the opinion that in the light of the legality principle, experimental legislation is reasonably robust given its legal basis,[122] but Ranchordás is more critical. She draws a connection between the principles of good science and principles of good regulation and argues that the legality of experimental statutory regulations is intrinsically bound up with their methodology. Related to that, she points out that experimental statutory regulations have been criticised because of their lack of an underlying systematic methodology, their casuistic nature and the limited validity of the results, which she maintains has contributed to the low acceptance of experimental legislation by the courts and legal academics.[123] However, the proposals she makes to improve the methodology of experimental statutory regulations suffer from the same shortcomings criticised above: they are still based on a top-down approach to evaluation that betrays a blind spot for bottom-up knowledge, although applied more precisely and consistently.[124]

3.4 Judicial law-making

As discussed in § 3.2, when legislation is formulated in abstract terms it is assumed that it will be interpreted more specifically by various actors, including the courts. Judges apply standards and goal-based regulation to concrete situations and in doing so make more specific rules. But the role of courts is not limited to that alone. Even when they apply more specifically formulated legal rules, they interpret the rules and make law. In this section we discuss the contribution made by judicial law-making to the robustness of technology regulation.

3.4.1 Judicial promotion of adaptive regulation

Thew courts have a good track record in flexibility and the capacity to adapt rules to new developments. Judges can often make quicker decisions on cases than the legislature can make new laws. Adaptivity is an intrinsic part of their work; in contrast to the legislature their job is to apply general rules to real situations. This means that it matters how judges do their job. Judges who keep strictly to the letter of the law will display less adaptability.[125] Purposive interpretation, in which not only the letter of the law but also the spirit of the law counts, gives judges more flexibility in a context of technological change.[126] The Court of Justice of the European Union (CJEU) often resorts to purposive interpretation.[127] Purposive interpretation is in principle possible for all types of regulation, but is facilitated by regulations that explicitly invite

[121] Idem, p. 1135.
[122] Idem, p. 1135.
[123] Ranchordás, 2021, p. 3–4.
[124] Idem, p. 16–18.
[125] Feteris, 2017, p.166.
[126] Moses, 2007, p. 279–281.
[127] See inter alia Brown & Kennedy, 2000, p. 330–331, 339; Dhooge, Franken & Opgenhaffen, 2015, p. 135–136.

it, or at least gives reason to do so, such as goal-based regulation and standards (see § 3.2.1) or laws that contain no solutions for new situations or which contradict one another.[128]

Various authors discuss the strong points of judicial law-making for promoting adaptivity in regulations. The first advantage attributed to the judicial interpretation of standards is that facts that come to light in legal proceedings and the interpretations by different courts generate new information after the standard has been implemented. This information guides the interpretation of standards and this interpretation may be changed by subsequent case law.[129] The second advantage that is mentioned is that information produced in legal proceedings costs less than obtaining it when drafting legislation, because parties in a dispute produce facts to support their case at no cost (whereas private parties generally do not submit factual statements to the legislature on their own initiative).[130] A third advantage of judicial law-making is that it involves a process of 'natural selection'. Good decisions by the courts have more chance of being confirmed on appeal and then followed by other courts, embedding them more firmly in the case law. In this view, poor decisions have less chance of holding up because there is a greater chance of continued litigation to get them overruled.[131]

3.4.2 Judicial promotion of legal robustness

The courts can not only contribute towards the adaptivity of the law, but are also eminently suited to safeguarding the legal robustness of legal rules. For example, it is their task if required to review regulations against legal principles such as legal certainty and legal equality.[132] They are therefore in the picture for both aspects of robust regulation: adaptivity and legal robustness.

That does not mean that adaptivity and legal robustness in court rulings are always perfectly balanced. Depending on the case, court rulings may sometimes stress safeguarding legal principles, while other rulings may make a stronger contribution to adapting the law to changing circumstances. In general, we could say that the task of judges as guardians of legal robustness, in combination with their predominantly reactive case-by-case approach, means that making changes to the regulatory regime via case law will more often be gradual rather than radical.[133]

3.4.3 Reservations concerning the role of judicial law-making

Despite the advantages attributed to judicial law-making, it is not a panacea. First, it is not always easy for judges to interpret rules or standards in accordance with their objectives. This is because the aim of legal rules is not always clear or can be interpreted in multiple ways, because regulations, certainly in a multilayered and multi-actor context like the EU, are the outcome of compromises and as such often have to reconcile multiple objectives which may in practice be incompatible.

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[128] Feteris, 2017, p.166.
[129] McGinnis & Wasick, 2014, p. 1039.
[130] Kołacz, Quintavalla & Yalnazov, 2019, p. 6.
[131] McGinnis & Wasick, 2014, p. 1027–1028.
[132] Philipsen, Stamhuis & De Jong, 2021; Cappelletti, 1981.
[133] Cf. Shapiro,1965.

Second, there are limits to purposive interpretation. Judges must still make a convincing case for their purposive interpretations by referring to the law (possibly including the preamble), while the phrasing and definitions used in the law impose certain constraints on the room for interpretation. The more precisely the rules are formulated, the more acute this problem becomes. Opinions on the legitimacy and separation of legislature and judiciary also determine the degree of flexibility judges can permit themselves to take.

Third, purposive interpretation does not always satisfactorily address the questions posed by technological developments, as shown by the ruling of the CJEU on modern forms of mutagenesis in case C528/16. In that case, the Court of Justice, as it frequently does, made a purposive interpretation, but this placed a strong emphasis on the protection objective of the regulations at the cost of the innovation objective.[134]

Fourth, the flexibility that judicial interpretation can offer should not be exaggerated, as became clear in § 3.4.2. It is mainly the most senior judges, at the EU level the Court of Justice, who are able to lend authority to a new interpretation of the rules, and that route cost time and involves significant hurdles.[135] Lower judges will be less comfortable with applying new interpretations and will tend to follow existing case law. If they do apply a new interpretation, it will usually have less far-reaching consequences and/or run the risk of being overruled in the final instance.

Fifth, in certain respects the judicial route is less manageable than the legislative route. The courts only have a say when a case comes before them.[136] And then it has to be seen what they do and which interpretation they consider acceptable. It cannot be taken for granted that they will make a judgement in line with societal demands.[137] The legislature can be lobbied and its decision-making is to a certain extent more transparent. The weighing up of conflicting societal demands, values and interests, which is particularly relevant when risks and opportunities are uncertain, is generally speaking more a job for the legislature, which represents a range of opinions as a result of democratic elections, whereas unelected judges are not supposed to choose sides and are less equipped to make such difficult decisions.[138]

Given these reservations, it is questionable whether encouraging judicial action, for example by formulating open standards, is a fruitful strategy. Neither is it clear in which situations legislators would be inclined to give the courts so much responsibility.

3.5 Regulation by regulatory agencies

The literature on adaptive and future-proof regulation assigns an important role to regulatory agencies. This term covers a range of government bodies which, as part of the executive, have delegated powers within a statutory framework or room for discretion to define specific rules for their field of competence. These bodies include government ministries and departments within them, and at the EU level the various directorates-general (DGs) of the European Commission. But the literature on the subject mostly concerns government bodies that have a more

[134] See Box 2.1.
[135] See e.g. Hoevenaars, 2018.
[136] Cappelletti, 1981, p. 46.
[137] Cf. McGinnis & Wasick, 2014, p. 1048
[138] Cf. Kołacz, Quintavalla & Yalnazov, 2019, p. 7–8; Cappelletti, 1981, p. 48–49.

independent mandate than ministries,[139] such as the National Institute for Public Health and the Environment (RIVM) and independent administrative authorities such as the Central Committee on Research Involving Human Subjects (CCMO), and at the EU level the European Medicines Agency (EMA) and the European Food Safety Authority (EFSA). In this section we discuss the potential of regulatory agencies regarding robust regulation.

3.5.1 The contribution made by regulatory agencies to adaptive regulation

The main advantage of regulatory agencies is that they can adapt regulations more quickly than taking the legislative route. The hurdles that have to be surmounted when amending legislation, such as consulting stakeholders and advisory bodies and obtaining political endorsement in Parliament, make this a time-consuming process that depends on many different actors for success. Moreover, obtaining political endorsement not only takes time, but also requires making compromises in the substance of the legislation, which may erode its adaptivity. This is all the more so for EU legislation, where the political process involves many more actors on multiple levels than in the national context.

Regulation by regulatory agencies, on the other hand, is subject to far fewer conditions and is not directly dependent on political approval.[140] For this reason, regulatory agencies are generally better able to make adaptive regulations than the legislature, in terms of both the content of the regulations and the speed at which they can be amended. Regulatory agencies are better able to take scientific advice on board because they are under less pressure to make political compromises when making rules.[141]

The latitude regulatory agencies have to set rules depends largely on the nature of the statutory framework within which they operate. Abstract legislation, especially when accompanied by an explicit delegation of broad regulatory powers, gives regulatory agencies considerable scope to make detailed rules.[142] But even when the legislation is formulated more precisely and/or it is not clear exactly what regulatory powers a regulatory agency has, regulatory agencies can acquire considerable leeway to make rules, although less clearly defined and legitimised – and possibly also heavily influenced by political circumstances. Greer and Trump point to the consequences of a multilayered democratic system such as the EU, which is characterised by much internal debate and whose course is determined by multiple actors not in a hierarchical relationship with each other.[143] The difficulty of establishing legislation in such a system can make it tempting to leave no open ends at all. When an occasion arises to revise the legislation, political actors feel under pressure to get their own political preferences written into the legislation as much as possible, precisely because the next opportunity could be a long time in the future. The resulting legislation is hardly adaptive, which can lead to the need for regulatory agencies that can provide the adaptivity missing from the legislation in lower order rules.[144]

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[139] In the English language literature, usually referred to as 'regulatory agencies'.
[140] Although they do operate with the political backing of a national government or, at the European level, the European Commission, which can be held accountable for the activities of regulatory agencies.
[141] Cf. Bennett Moses, 2007, p. 277–278; Greer & Trump, 2019, p. 511–512.
[142] See § 3.2.2.
[143] In particular the governments of the member states, the European Commission, the European Parliament and the Court of Justice of the European Union, but also the national parliaments and national courts.
[144] Greer & Trump, 2019, p. 511.

The perceived need for adaptive regulatory agencies in such situations, however, does not automatically mean that there is room for adaptivity. This requires legislation that includes open standards, ambiguities or loose ends which are sufficiently open to adaptive interpretation by a regulatory agency, or the most specific rules must have been given a more flexible status.[145] An important factor is what type of formal mandate and political support an agency obtains through the way it operates within conflicting expectations and interests. On this Greer and Trump say the following:

> Not all regulators are adaptive, but successful ones establish a reputation for competency and a unique ability to satisfy multiple principals .... Viewed over time, it means that an agency or group of regulators draws on international, scientific, bureaucratic and political resources to demonstrate that they will competently and predictably pursue a certain kind of objective, without angering important principals and while adapting to new technologies. This means that a large number of principals trust them to carry out a task that they largely define, so that there is a coalition to defeat any effort to constrain their autonomy. Once established with a broad mandate in rigid law that permits adaptation within its legal scope, it is difficult to constrain them without legislative change, and all that agency administrators have to do to is show a normal level of political adroitness to avoid creating a crisis that could lead the multiple principals to agree on legislative change.[146]

Although agency-based regulation does not depend directly on political approval, regulatory agencies do need to take political realities into account if they are going to be successful and adaptive. They should also involve stakeholders in the process of making and amending regulations. This is an administrative requirement and in the literature it is recommended that generous opportunities for stakeholder involvement should be made available. The main reasons for this are that it can strengthen the democratic legitimacy of and support for agency-based regulation and that the quality and adaptivity of the regulations is improved by the input of social and technological knowledge.[147] Different gradations of stakeholder involvement are found in the literature and in practice, including situations in which regulatory agencies work with, or delegate much of the regulatory work to, stakeholders such as industry associations, research institutes and non-governmental organisations representing public interests. Situations in which regulatory organisations encourage stakeholders to make their own regulations are referred to as the facilitation of 'soft law'.[148] When at least a few representatives from industry and technological research are also involved, there is self-regulation. The main advantage of this is that it is the best way to keep the rules updated with the latest knowledge.

3.5.2 Regulatory sandboxes

A special form of interaction between regulatory agencies and industry actors and groups working in technological research is the 'regulatory sandbox'. This is a form of experimental regulation without a legislative basis, but initiated by regulatory agencies. In a regulatory sandbox, agencies give private parties temporary exemption, usually also restricted to a specific location, from the existing regulatory framework with an experimental objective: to investigate how a more flexible form of regulation could work out for certain technological applications or

[145] E.g. by formally putting them in an annex to the legislation.
[146] Greer & Trump, 2019, p. 511–512.
[147] See inter alia Hagemann, 2018; Bonnin Roca, 2024.
[148] See inter alia Hagemann, 2018; Hagemann, Huddleston Skees & Thierer, 2018; Reichow, 2015.

how new developments can best be regulated. Both the agency and the private parties have a clear interest in the outcome of such a process. In practice, regulatory sandboxes often lead to a form of cooperation between the regulatory agency and the private parties.[149]

In theory, regulatory sandboxes differ from experimental legislation. In the latter, the experiment must be explicitly stated in the legislation; in the former the experiment is carried out as a departure from the legislation.[150] To make regulatory sandboxes possible, regulatory agencies must therefore have a firm standing and take a broad view of their discretionary powers.

In practice, the difference between regulatory sandboxes and experimental legislation is not always so clear cut. First, regulatory sandboxes can also be considered as an opportunity for experimentation in which an agency does not so much depart from the legislation as from its own regulatory framework for interpreting standards laid down in the legislation. The more abstract the wording in the legislation, the smaller the chance that an experimental deviation from the regulatory framework of the regulatory agency will come into conflict with the overarching legal rules. Second, there are also hybrids between experimental legislation and regulatory sandboxes. For example, the proposal for a new EU Regulation on the regulation of medicinal products contains a legal provision for regulatory sandboxes, complete with the conditions those sandboxes must meet.[151] Lastly, evaluation mechanisms are considered to be as crucial for regulatory sandboxes as they are for experimental regulation. Without evaluation, it is hard to draw general lessons from an experiment with potential adjustments to the regulatory framework.

3.5.3 Reservations concerning the role of regulatory agencies and the use of regulatory sandboxes

Based on the literature, several reservations can be made regarding the contribution regulatory agencies can make to robust regulation. One reservation was raised in § 3.2.2: it is constitutionally and democratically questionable to delegate considerable regulatory powers to regulatory agencies, because the primary responsibility for regulation lies with the legislature and democratic oversight is also at that level.[152] This criticism carries even more weight when regulatory agencies facilitate regulatory sandboxes that do not have a statutory basis. According to Philipsen and others, these are particularly fragile from the perspective of the legality principle:

[149] See inter alia Handrlica, Sharp & Nešpor, 2023; Philipsen, Stamhuis & De Jong, 2021; Ranchordás, 2021; Sherkow, 2022. See Engels, Wentland & Pfotenhauer, 2019 on the related concepts of 'test beds' and 'living labs'.
[150] Philipsen, Stamhuis & De Jong, 2021.
[151] Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC (COM (2023)192 final) and Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, (COM (2023) 193 final) recital 133 and Art. 115.
[152] Inter alia Bennett Moses, 2007, p. 278; Westerman, 2014, p. 129, 134.

> Executive authorities establishing a sandbox often make use of discretionary powers granted to them, although when granting these powers, the legislature almost never anticipated the use of the discretionary powers for the introduction of experimental policies.[153]

However, criticism of the constitutional and democratic shortcomings of agency-based regulation can be qualified somewhat. In the American literature this criticism can be partly understood in the context of the battle for legislative power between the states and the federal government. Regulatory agencies are often part of the federal government and criticism of their powers or the exercising of those powers may stem from the view that democratic decision-making should lie primarily with the states.[154]

At the same time, similar criticism is also expressed in a European or Dutch context,[155] but this criticism can also be challenged. Both the Netherlands and the EU have a long tradition of layered regulation in which formal legislation lays down the basis for detailed regulations at lower tiers of government, and in which regulatory agencies are given the legal authority to make rules themselves. From a formal legal perspective, such arrangements have by now proved their worth.

Moreover, it is not the case that regulatory agencies develop rules entirely on their own. Ultimately, they fall under the responsibility of a minister who can be held politically accountable, and they are required by law and by their own policies to consult or engage more fully with a range of stakeholders. Whether this is a suitable substitute for direct control by democratic bodies depends on the specific circumstances.

The scope for consultation and other forms of participation provided by regulatory agencies gives rise to two further observations. First, consultation procedures can become so elaborate that they pose a threat to the adaptive advantage of agency-based regulation.[156] Second, when stakeholders are closely involved in drafting rules, effectively working alongside the regulatory agency, their roles may become blurred. Such role confusion can create uncertainty about the extent of the agency's public responsibility, for example regarding the consequences of experiments conducted in a regulatory sandbox.[157]

Lastly, the reservations concerning the vulnerability of experimental legislation from the point of view of legal certainty and legal equality discussed in § 3.3.2 apply even more to regulatory sandboxes. This is because insofar as regulatory sandboxes conform to the ideal type defined in the literature, they rely on the discretionary powers of regulatory agencies and have no firm statutory basis, which makes them particularly exposed to legal challenges by people and businesses.[158]

[153] Philipsen, Stamhuis & De Jong, 2021, p. 1135.
[154] With thanks to Prof. Evert Stamhuis for this insight.
[155] E.g. by Westerman, 2014.
[156] McGinnis & Wasick 2014, p. 1039–1040; Nielson, 2018.
[157] Philipsen, Stamhuis & De Jong, 2021, p. 1135.
[158] Philipsen, Stamhuis & De Jong, 2021, p. 1135–1136.

Part II Case studies

4 Approach to the case studies

4.1 The case studies and the theoretical framework

In this part of the study the insights into grey areas discussed in Chapters 2 and 3 are empirically tested and refined in two case studies of biotechnology regulation in practice. Findings from a case study in green biotechnology and one in red biotechnology were analysed to identify how grey areas manifest in these fields (problem analysis) and which approaches towards more robust regulation are best suited to the specific form the problem takes in these contexts (solution strategies).

In Chapter 2 (§ 2.3.2) we saw that for the analysis of the case studies we followed the proposal by Poort et al. (2022) to structure stakeholder involvement in different phases. We analyse the case studies in two steps: 1) problem analysis and 2) solution strategies. In the first step, which is mainly descriptive, the various layers of the problem and diversity of opinions are identified and analysed (see Box 4.1). For a good analysis it is important that the knowledge domains relevant to the legal decision-making are consulted (§ 2.3.1). Besides technological developments, social and political developments can also influence the nature and complexity of the problem. This led to the following key issues for the problem analysis.

Box 4.1 Step 1: Problem analysis (grey areas)

1a) What opinions do stakeholders have concerning the robustness (or lack of it, including legal boundaries and obstacles) of the legal framework? 1b) What are the causes and explanations for the robustness (or lack of it) of the legal framework? 1c) What types of knowledge are required for this analysis?

The second step explores the possible solution strategies (see Box 4.2). Chapters 5 and 6 mainly discuss the findings from the interviews. What changes do the respondents in the two case studies want to see, and to what extent do these impact the robustness of the regulatory framework?

As stated in Chapter 2, the feasibility of some solution strategies depends on political will. The feasibility of the solution strategies and on the relevant knowledge domains is explored in more detail in Part III. In Chapter 7 the results of the case studies are assessed against of the identified solution strategies within the theoretical framework formed by the possible solution strategies identified in Chapter 3. In addition, the legal and political feasibility of the proposed solutions and their practical implications in relation to EU legislation and legislative proposals are investigated. This leads to the following points for consideration in the analysis of the solution strategies.

Box 4.2 Step 2: Solution strategies (robustness)

2a) What changes do the stakeholders in this case want to see? 2b) How far do these needs affect the robustness of the regulations? 2c) How should the legal framework be adapted to properly address these needs? 2d) How do the desired changes relate to EU or other legislative proposals? 2e) What types of knowledge are required for this?

The structure of Chapters 5 and 6 also reflects these steps. They begin with a background description of the case study, followed by an analysis of the grey areas and finish with a description and examination of possible solution strategies.

4.2 Selection of case studies

The case studies were selected on the assumption that these biotechnology applications could be in a grey area or could cause a grey area in the legislation.

To obtain the widest possible range of contexts within biotechnology, the first selection criterion was the diversity of applications. To this end we chose case studies from green biotechnology and red biotechnology, because these two fields are subject to different political and societal values.

The second selection criterion concerned the diversity of grey areas. Here too, we attempted to obtain the widest possible picture of the dilemmas within biotechnology, as grey areas can manifest in multiple ways and throw up obstacles at different levels. The legal definition of an organism consists of several elements that are open to debate, so the selected case studies relate to different elements of the definition and throw light on a diversity of topics.

The third selection criterion was the urgency of the need to address the problem of grey areas. The first case study concerns the use of cisgenesis in agriculture. This case study is set against the background of forthcoming new legislation for new genomic techniques (NGTs), which may introduce changes to the legal classification of cisgenesis. Cisgenic crops offer the possibility of responding more quickly to climate change by modifying existing agricultural varieties with genes from crossable relatives. Experts maintain that by remaining within this gene pool, the risks associated with cisgenic varieties will be within the same range as the risks of conventionally bred varieties, which have a long history of safe use.

The second case study concerns the development of self-amplifying messenger RNA vaccines (samRNA vaccines). Regular mRNA vaccines are not covered by the GMO legislation because mRNA is not considered to be an organism and therefore cannot be classified as a genetically modified organism. During the response to the Covid-19 pandemic these regular mRNA vaccines underwent rapid development. SamRNA vaccines are still being developed, but can elicit a more vigorous immune response. It may therefore not be possible to use this type of vaccine efficiently in response to potential future pandemics. They have the ability to *replicate* the RNA that codes for the target gene within the cell; the question is whether or not this brings them within the scope of the GMO legislation. This raises questions about the definitions of an organism and a GMO.

4.3 Research methods

Two research methods were used to describe and analyse the case studies. The first method was a qualitative document analysis of policy documents, research reports, knowledge websites and legislation relevant to both case studies. In both case studies, national and EU legislation determines the legal framework within which the chosen case is regulated, and so the national and EU legislation, legislative proposals and associated policy documents were included in the analysis. The research reports were mainly limited to the national context, because grey areas usually arise in a national context and from the application of the (national or EU) legal framework in this national context. These research reports were used to obtain a better understanding of the technology and the context within which a grey area arises.

The second research method used for this part of the study was qualitative empirical research. Semi-structured interviews were held to identify and explore how stakeholders view the problems of the GMO status of cisgenesis in agriculture and of samRNA vaccines. For each case study, eight to ten interviews were held with various experts, policy officers and representatives from advisory bodies, and for green biotechnology also opponents of the use of biotechnology. As this was not a quantitative empirical research method, the analysis of the case studies does not contain any results from which broad general conclusions can be drawn. The aim of the interviews was first of all to obtain a better picture of practical issues and the obstacles encountered that do or do not make the case study a grey area. The interview questions also sought to explore the need for changes to the regulations felt by stakeholders and examine possible solution strategies.

4.4 Interviews

Eight to ten interviews of one hour were held for each case study. The selection of respondents was made in consultation with the supervisory committee. The aim was to select the broadest possible representation of all the relevant actors. For the case study on the regulation of green biotechnology, various respondents were invited from the plant breeding sector and from policy officers at the Ministry of Agriculture, Fisheries, Food Quality and Nature (LVVN) and the Ministry of Infrastructure and Water Management (IenW). In addition, a member of COGEM's Subcommittee on Agriculture was interviewed and a senior adviser from the National Institute for Public Health and the Environment (RIVM). To include a different perspective in the analysis, a respondent from the organic farming sector was also interviewed. Two of the respondents in the 'green' case, the senior adviser from RIVM and the IenW policy officer, were also questioned on the regulation of red biotechnology. For the 'red' case, interviews were also held with several experts with experience of the development of samRNA vaccines or similar vaccines, one of whom is a member of COGEM's Subcommittee on Medical and Veterinary Aspects. In addition, interviews were held with a few respondents familiar with the theory and practice of environmental risk assessment and the authorisation procedure.

The interviews were semi-structured. The same topic list was used as the basis for each interview, divided into questions for identifying and analysing grey areas and questions exploring solution strategies for making the regulations future-proof (the steps in § 4.2). More or less time was devoted to certain questions depending on the expertise of the respondent. All the interviews were held within a three-week period, with insights and suggestions from previous interviews included in some of the later interviews. During a few of the interviews,

some time was devoted to asking about certain concepts to obtain a better understanding of the technology and its applications. The explanations were also included in the analysis of the case studies.

Appendix 1 and 2 contain the topic lists for the case studies. Appendix 3 contains an overview of the respondents per case study. The interviews were analysed and stored on a secure platform (Yoda) and are only available to the researchers.

5 Grey areas in green biotechnology: cisgenesis in agriculture

5.1 Background

5.1.1 Background to the DuRPh project

In the DuRPh project, which ran from 2006 to 2015, Wageningen University & Research (WUR) developed a cisgenesis technology to create potato varieties with more lasting resistance to *Phytophthora infestans*, the main potato disease, than is possible by conventional breeding methods. The project was funded with public money from the *Fonds Economische Structuurversterking* (Economic Structure Reinforcing Fund, which was financed with state revenues from natural gas extraction) and carried out for the Ministry of Agriculture, Nature and Food Quality.[159] DuRPh can be understood as an attempt to kickstart biotechnology innovation again following several dry years. The de facto moratorium on new approvals of genetically modified crops upheld by various EU countries since 1998 came to an end in 2004.[160] They used this moratorium to force a tightening of the EU authorisation regime,[161] the adoption of new rules for labelling and tracing genetically modified products,[162] and the replacement of scientific committees which until then had advised the European Commission on the approval of genetically modified products, and which they did not trust, by the newly established European Food Safety Authority (EFSA).[163]

In the period the moratorium was in force, the public debate on genetically modified crops and food products heightened and shifted towards the centre ground of society, accompanied by increasing consumer familiarity with genetically modified foods. The main objections to 'green' gene technology were its perceived unnaturalness (in particular the crossing of species boundaries in transgenesis, then the dominant form of genetic modification) and the associated risks to the environment ('contamination' of conventional or organic crops) and human health. Concerns about the possible health effects of genetically modified food were fuelled by the BSE crisis, which erupted in 1996. The BSE crisis had nothing to do with gene technology, but was readily adopted as part of the argument because it illustrated how risky 'unnatural meddling' with food can be and it eroded public trust in government and scientific advisory committees entrusted with guaranteeing food safety, just when the first imports of genetically modified crops arrived in Europe. Besides naturalness and risks, consumer choice was a prominent theme in the public debate on gene technology, the argument being that consumers must always have the choice of non-genetically modified food. The new EU labelling and tracing rules were meant to address at least some of these concerns.

In this period, environmental organisations took advantage of the increased public awareness of genetically modified food by publishing lists of products they claimed were produced with gene technology. Under this pressure, supermarkets and manufacturers, fearful of falling sales and reputational damage, began removing any genetically modified ingredients from their

[159] https://www.wur.nl/nl/project/durph-1.htm (last accessed on 27-01-2025)
[160] Concerning the context in which the moratorium came about, see : Kortleven, 2013, § 5.3.1 and § 5.3.3.
[161] Via the replacement of Directive 90/220/EEC by Directive 2001/18/EC.
[162] Regulations 1829/2003 and 1830/2003.
[163] Via Regulation 178/2002. For a more extensive discussion of the period, see Kortleven, 2013, p. 299–304.

products. By the beginning of the 2000s, genetically modified food products had largely disappeared from the shelves.

In this gene technology unfriendly environment, some manufacturers of genetically modified products did not wait to see if the ending of the moratorium would lead to an improvement in their situation, but discontinued or drastically reduced their activities in Europe, and in some cases relocated to the United States. Other companies and research institutes responded to the political barriers and public agitation by deciding to develop new forms of genetic modification which they expected would be less controversial, such as cisgenesis.[164] These types of initiatives could count on keen interest from the Dutch government, which had little sympathy for the attitude of the moratorium countries, and which after the ending of the moratorium felt it was high time to exploit the potential of gene technology, as far as the new stricter rules would allow.[165]

5.1.2 Design and purpose of DuRPh

This was the context within which the DuRPh project was initiated. The project investigated how to make potato varieties durably resistant to *Phytophthora* by cisgenesis. Cisgenesis is the transfer of traits between crossable plant species by means of genetic modification. In contrast to transgenesis, no foreign DNA is introduced and in theory the same result could be achieved by conventional breeding, although with much more time and effort.[166] The DuRPh project aimed to make potatoes resistant to *Phytophthora* by inserting multiple resistance genes (R genes) from wild-type potato species in varying combinations. This approach has significant advantages over conventional breeding methods. It generally takes decades to make a qualitatively good potato with one type of resistance by conventional breeding, let alone with multiple resistances, because the wild-type potato used as the basis for the resistance also brings with it a variety of undesirable characteristics which then have to be removed by backcrossing. The years it takes to introduce resistance this way bear no relation to the adaptability of *Phytophthora*, which can easily get round a single resistance gene. Given this uneven battle, conventional growers cannot be confident about the resistance of their potatoes, especially in a very wet season, and so they have to resort to large applications of fungicides. The promise of the DuRPh approach was a quicker and more effective way of making potatoes resistant to *Phytophthora*, and moreover, because of the use of multiple and varying R genes, resistant in a way that would be much harder to break down.

Achieving durable resistance to *Phytophthora* was one goal of the project, but it was more ambitious than that alone. The project also intended to stimulate and facilitate innovation in genetic modification in general in the Netherlands, while at the same time encouraging public debate about innovative genetic technology.[167] The choice of cisgenesis was an attempt to take the sting out of the objection that genetic modification is unnatural, and a conscious decision was made not to use marker genes, which had become controversial in the public and political debate. By focusing on promoting resistance to the most important potato disease, which could considerably reduce the dependence on expensive and harmful pesticides, the value and sustainability benefits of genetic modification could be demonstrated and opened up for

[164] Kortleven, 2013, p. 297.
[165] Kortleven, 2013, p. 304.
[166] Schouten, Krems & Jacobsen, 2006.
[167] Haverkort et al., 2016.

discussion. It was also hoped that widespread communication with a broad and diverse public on the project would increase public acceptance of these types of applications of genetic modification, or in any case that the transparency of the project would lead to growing confidence in the developers of gene technology and a shift in public perception of the opportunities and drawbacks. Lastly, it was hoped that this tangible application of cisgenesis (the public were permitted to visit the field trial site) would not only feed the public debate, but could also have an influence at the political level to relax the authorisation regime which had been tightened up in 2001, at least for the products of cisgenesis.[168]

5.2 Problem analysis

5.2.1 The outcome of DuRPh

The researchers in the DuRPh project are largely positive about the outcome of the project. The researchers say they have been successful in making potato crops durably resistant for far longer than previously possible.[169] The project demonstrated that a form of resistance is feasible that can reduce the use of pesticides by 80%,[170] and therefore that the contribution this technique can make to sustainable solutions is not just hypothetical. The project has also become a concrete example in policy visions on innovative plant breeding in the Netherlands. This was confirmed in the interview with a senior policy officer for biotechnology at the Ministry of LVVN, who said that the DuRPh project is still regularly referenced in policy circles as a concrete example of the contribution innovative plant breeding can make to sustainability.

In addition, the researchers are positive about the contribution the project was able to make to the public debate, which has been increasingly about the positive traits of DuRPh potatoes, while the abstract discussion of genetic modification has moved to the background. Another respondent was more critical about the public relations on the DuRPh project, because he felt the societal benefits in terms of sustainability could have been more prominent. He said this is perfectly illustrated by a piece on the project website, which began by listing the advantages of reduced costs for the breeder, whereas it would have been better to highlight the advantages to society as a whole.[171]

According to the researchers involved in the project, there was little or no public resistance; the field trials needed minimal protection and the trial site was visited by hundreds of people without any problems.[172] However, the project did not come out entirely unscathed: in 2012, halfway through the project, two DuRPh trial fields were vandalised, not unusual at that time for field trials of genetically modified crops. No-one claimed responsibility for the actions.[173] Some environmental groups were critical, although there were also constructive contacts. In the interview with the team leader of applied ecology at WUR, who was responsible for communication with the public, it emerged that a Greenpeace representative was present at public events and had little objection to the research in itself. However, he stressed that the

[168] Interview with plant breeding researcher, WUR; interview with team leader, applied ecology, WUR; Haverkort et al., 2016. See also Jacobsen & Schouten, 2008.
[169] Interview with plant breeding researcher, WUR; interview with team leader, applied ecology, WUR.
[170] Haverkort et al., 2016.
[171] Interview with member of the Subcommittee on Agriculture (ScL) COGEM.
[172] Haverkort et al., 2016, p. 59.
[173] *Aanhangsel Handelingen II* 2012/13, nr. 207; Kortleven, 2013, p. 305.

potatoes should not be present in the environment. Also critical of the principles underlying the project was the director of the organic supermarket Odin, who we interviewed. She argued that instead of seeing the resistance/adaptability dynamic of the disease as an arms race that breeders should engage in with more efficient weapons, the problem analysis should include how the intensive nature of conventional agriculture increases susceptibility to crop diseases.[174] Nevertheless, the DuRPh project also aroused the interest of organic breeders.[175]

One goal of the DuRPh project that has not yet been achieved is changing the legislation, although the researchers we interviewed do think that the project may have had an influence on the development of the European Commission's proposal on NGTs, which at the time of writing is still being negotiated with the member states.[176] One of the researchers described how she was interviewed by someone from the European Commission's Joint Research Centre, which had an input to the Commission's study on the status of NGTs in preparation for the legislative proposal on NGTs.[177] This legislative proposal on NGTs explicitly includes cisgenesis.[178] However, as long as the legislative proposal has not become law, potatoes containing genes introduced using the DuRPh technology may not be cultivated in the EU. Whether this will be permitted when the proposal has become law is treated in § 5.3.

5.2.2 The legal status of DuRPh potatoes

The respondents were all convinced that cisgenic products, including the DuRPh potatoes, fall under the authorisation regime in Directive 2001/18/EC. However, when the DuRPh project was launched this was not a foregone conclusion as the legal status of cisgenesis,[179] which was only developed after Directive 2001/18/EC came into force, was still up for discussion. The uncertainty underlying this discussion was in part due to the ambiguous definitions in the directive, where a GMO is defined as an organism 'in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination' (Art. 2(2)). In practice, the criterion of 'naturalness' can be interpreted in a variety of ways. The annex to the directive gives a more detailed explanation on which techniques are and are not considered to lead to a GMO, with non-limitative lists, including techniques which lead to a GMO but are still exempted from the scope of the directive. What does this mean for organisms modified by cisgenesis? On the one hand, an interpretation in which such organisms do not fall within the definition of a GMO in Art. 2(2) is defensible, because the same result could, at least in theory, have been achieved by natural means through the more cumbersome and lengthy process of crossing. On the other hand, however, it can be argued that cisgenesis as used in the DuRPh project uses the same type of technique as transgenesis, which in Annex I A Part 1 of Directive 2001/18/EC is explicitly stated to a be a technique that leads to a GMO.

However, the publications on the DuRPh project reveal that initial expectations were not geared so much towards an interpretation of the GMO definition which would exclude cisgenic organisms, but to the type of exemption given to mutagenesis in Directive 2001/18/EC. This

[174] Interview director of Odin.
[175] Bergmans et al., 2020, p. 76.
[176] COM(2023) 411 final.
[177] EC (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 (SWD(2021) 92 final).
[178] See Art. 3(2) and 5 COM(2023) 411 final.
[179] See e.g. *Kamerstukken II* 2011/12, 27 428, nr. 230.

technology, in which organisms are genetically modified by irradiation or treatment with chemicals, is listed in Anex I B as a technique of genetic modification, but is nevertheless excluded from the Directive. In 2018 the CJEU ruled that this exclusion applied only to conventional mutagenesis techniques that already existed when the Directive came into force, on the grounds of a proven history of safe use.[180] This ruling makes the possibility of an exclusion for cisgenesis, although not explicitly mentioned in the Court's ruling, even more unlikely.

According to DuRPh project participants, cisgenic potatoes should be treated differently from transgenic organisms because of the difference in naturalness and the positive characteristics of cisgenic potatoes, especially because conventional potato varieties require the use of many more pesticides. The importance attached to a legal exemption was related to the fact that authorisation under the regime in Directive 2001/18/EC, even after the end of the de facto European moratorium on new gene technology products, had proved to be a costly and hard to negotiate route, not least because several member states remained opposed on non-safety grounds.[181] Moreover, labelling as a GMO product approved under Directive 2001/18/EC would be a stigma with economic consequences. One of the researchers maintained that a GMO label would mean that large numbers of people would not want to eat it and no farmer would be willing to grow it, partly out of fear of activists.[182]

In short, the problem encountered under the current legal framework is not so much that there is legal uncertainty about the status of applications of cisgenesis, but that stakeholders feel the legal framework is too restrictive given the opportunities presented by and limited risks of cisgenesis.[183] They claim that it unnecessarily stifles innovation and excludes the sustainability benefits made possible by the DuRPh project, and that the restrictive nature of the legal framework is largely due to the political reality surrounding its application.[184]

The organic/biodynamic sector, and particularly the biodynamic farming community, is less unhappy with the status quo. There are three arguments for this. The first is an argument of principle against cisgenesis, felt most strongly in the biodynamic farming community, because, like other forms of genetic modification, cisgenesis interferes directly in the DNA of an organism and does not respect 'the integrity of the cell'.[185] This is a different point of principle than usually found in Christian circles, as evidenced by the position of the ChristenUnie (Christian Union) political party. They do have objections to 'crossing species boundaries', as is the case with transgenesis, but have little or no objection to cisgenesis, because only crossable plant species are used.[186]

The second argument is a question of coexistence, which is more a case of risks and economic interests. The fear is that approval of cisgenic crops for cultivation brings the risk of outcrossing

[180] See Box 2.1 in Chapter 2.
[181] Interview with team leader, applied ecology, WUR; see also Kortleven, 2013; Mampuys, 2021.
[182] Interview with team leader, applied ecology, WUR.
[183] See e.g. interview with policy officer, Plantum.
[184] Interview with project manager sustainable future, hollandbio; interview with policy officer, Plantum.
[185] Interview with director of Odin; interview with director of Plantum; interview with senior policy officer for organic agriculture, LVVN; interview with programme director, hollandbio.
[186] Interview with team leader, applied ecology, WUR.

with organic crops, making them unsaleable.[187] The respondents from hollandbio countered this by saying that the organic sector's argument of coexistence amounts to claiming exclusive rights to existence: organic crops may be grown, so cisgenic crops may not be grown. In this case, the freedom to choose organic products means no freedom of choice for breeders, farmers and consumers to develop, grow or consume cisgenic products.[188]

The claim that important sustainability gains can be made with DuRPh does not impress the director of Odin, who countered it with the third argument. She contended that the route to more sustainable resistance and the use of less pesticide in potato cultivation should not be genetic modification, but more fundamental changes to an intensive agricultural system that is exhausting the earth.[189]

5.3 Solution strategies

This section discusses the solution strategies for the encountered problems and grey areas in this case study. The legislative proposal for NGTs being negotiated by the member states plays a prominent role in the discussion, because some of the respondents claim it contains solutions, while others maintain it has drawbacks compared with their preferred solutions.

5.3.1 Goal-based regulation and reduction of technology specificity

The most radical solution strategy for robust regulation of cisgenesis and other NGTs raised in the interviews is to not focus on specific technologies, but rather on the possible risks of technological applications or on the interests and objectives served by regulation. One researcher and COGEM member said that the level of risk associated with a crop, for example because of its crossability or toxicity, depends on the traits that can also result from conventional breeding or spontaneous mutations. In risk terms, this researcher says, there is no reason to have a separate regulatory regime for the products of genetic modification or gene editing.[190]

However, it works both ways. In the legislative proposal for NGTs, certain NGT crops are put on a par with conventional crops and on that basis are exempt from the GMO authorisation regime. To be included in this category 1, NGT crops may contain no more than 20 genetic changes of certain specified types of modification compared with conventional crops.[191] However, according to this researcher, the safety of a crop does not depend primarily on the number of changes, but the type of changes: which gene has been altered, how has it been modified and what are the resulting changes in the characteristics of the crop? This means that it cannot be categorically stated that crops with fewer than 20 genetic changes are safer than crops with 30 changes.[192] Another respondent countered that a maximum of 20 changes may be arbitrary, but any limit is arbitrary and inevitably means that there will be some cases that fall just outside. Abandoning a limit would have the disadvantage of more uncertainty.[193]

[187] Interview with director of Odin.
[188] Interview with project manager and programme director, Hollandbio.
[189] Idem.
[190] Interview with member of ScL COGEM.
[191] Chapter II and Annex I of the NGT legislative proposal (COM(2023) 411 final).
[192] Interview member of ScL COGEM.
[193] Interview with senior advisor on gene technology and biological safety, RIVM.

Other respondents proposed the possibility of formulating regulations more in terms of the objectives and interests to be protected, in the spirit of 'how do we view agriculture, and what do we want from it?'[194] or something more concrete such as health, safety and sustainability.[195] At the same time, a disadvantage they mentioned is that these values are portmanteau concepts and what they mean in practice may be subject to considerable debate.[196] The legislative proposal for NGTs does contain a more specific operationalisation of sustainability. NGT crops in category 2 – all NGT crops that do not fall in category 1, and which remain subject to the GMO authorisation regime – may qualify for a more lenient authorisation process if they meet certain sustainability criteria.[197]

However, this way of putting sustainability first is inconsistent with the suggestion made by respondents from the Hollandbio advocacy group to reformulate the regulations from the perspective of sustainability and other values, because the sustainability criteria for category 2 NGT crops are a condition for approval (albeit in a simplified procedure), while conventional crops are not subject to these sustainability criteria for approval. In the view of these respondents, a comprehensive reform of the regulations into a more goal-oriented regulatory regime should be coupled with abandoning a separate regime for genetically modified products:

> Drop the technological component entirely. Science is advancing and cannot be anticipated. We are now [in the NGT proposal] again focusing on technologies. And the modernisation [of the legislation] is taking so long, you can bet that by the time it's completed it will already be out of date.[198]

Several respondents expressed a relativisation of the difference between products of genetic modification or gene editing and products of conventional breeding as a preference for a product-based approach over a process-based approach.[199] Instead of the current EU and Dutch regulatory regime in which products resulting from genetic modification (process) fall under a separate regime, they prefer a system which looks at the characteristics of a product independently of the way in which it is produced. According to some respondents, this a condition for creating a truly robust and future-proof regulatory regime, although they did acknowledge that such a change to the current system is not realistic, at least in the foreseeable future.[200]

Some are aware of the drawbacks of a product-based approach, such as those that apply in the United States and Canada.[201] A consistent product-based approach does not necessarily mean that products of genetic modification would be exempt from any form of risk assessment, but that products of genetic modification and conventional products would be subject to the same type of assessment. However, for conventional products that could mean a higher approval

[194] Interview with senior policy officer for biotechnology, LVVN.
[195] Interview project manager and programme director, hollandbio; interview with policy officer, Plantum.
[196] Interview with programme director, hollandbio.
[197] Chapter III and Annex III COM(2023) 411 final.
[198] Interview with programme director, hollandbio.
[199] Interview with project manager and programme director, hollandbio; interview with member ScL COGEM; interview with team leader, applied ecology, WUR; interview with plant breeding researcher, WUR; interview with director and policy officer, Plantum.
[200] See e.g. interview with project manager and programme director, hollandbio.
[201] For more on these drawbacks, see COGEM, 2019.

threshold, with inevitable consequences. One respondent pointed to the Canadian system in which conventional crops have to undergo a safety check, unless they are a product of standard hybridisation. In the European context, such a system could mean that many more crops would have to undergo a safety check: in the Netherlands alone, there are more than a thousand new varieties each year. This would put an enormous strain on the authorisation system and lead to even longer delays.[202]

The preference for a product-based approach is at odds with the fact that some members of the public object in principle to interventions at the cellular level through genetic modification and gene editing. In this view, which can be characterised as deontological,[203] genetic modification techniques differ fundamentally from conventional breeding techniques, regardless of whether the products of the two techniques are similar.[204] Supporters of this viewpoint cannot be convinced by arguments about the safety of NGT crops or a consequentialist emphasis on the sustainability benefits of NGTs,[205] because these types of arguments bypass the arguments of principle against genetic modification and NGTs.

The civil servants we interviewed took as given the existence of different world views and accepted this as a point of departure for policymaking. They considered the government to be the ideal guardian of a diverse agricultural system in which innovation via NGTs should be promoted, while at the same time ensuring a place for an organic sector free of NGTs.[206] A different approach to the organic farming sector would in any case run counter to the statutory prohibition of the use of GMOs in the organic sector, which in the legislative proposal for NGTs is explicitly declared to apply to the use of all NGTs.[207] The possibility of permitting category 1 NGT applications in the organic farming sector has in fact been considered by the European Commission, but was rejected because the use of NGTs is incompatible with the current definition of organic production in Regulation 2018/848 and because of objections from the organic sector.[208] The difficulty of keeping NGT products and organic products apart in practice is recognised by both civil servants and representatives from the organic farming sector and biotechnological sector.[209] To do this as effectively as possible, a separate regime for NGTs seems unavoidable, not primarily for safety reasons, but to safeguard the existence of the organic sector and do justice to fundamental objections within part of the plant breeding sector and the population.[210]

[202] Interview with director of Plantum.
[203] Interview with team leader, applied ecology, WUR.
[204] Inter alia, interview with the director of Odin.
[205] Idem.
[206] Interview with senior policy officer for biotechnology and senior policy officer for organic agriculture, LVVN; interview with policy officer for safety of biotechnology, IenW (policy officer A, IenW)
[207] Recital 23 and Art. 5(2) COM(2023) 411 final.
[208] COM(2023) 411 final, p. 11.
[209] Interview with senior policy officer for biotechnology and senior policy officer for organic agriculture, LVVN; interview with policy officer A, IenW; interview with director of Odin; interview with project manager and programme director, hollandbio.
[210] Cf. Bennet Moses, 2013, p. 15, as mentioned in § 3.2.1, on moral objections as a reason for technology-specific regulation.

5.3.2 Derogation and destigmatisation

In the absence of the possibility of a product-based approach, many proponents of the use of NGTs we interviewed would be content with less far-reaching solutions. In their view, one important solution was to deregulate and destigmatise cisgenesis and other NGTs. Under the current regulatory framework, NGT products are considered to be GMOs and, as mentioned above, the GMO authorisation procedure for new products in green biotechnology is an almost impassable obstacle course. The products that do successfully negotiate this process still face the stigma attached to the GMO label. Various respondents argued that crops and food products that have to carry this label are not economically viable.[211]

To give products of cisgenesis and other NGTs a chance, it will therefore be necessary to relax the current authorisation procedure and remove the stigma attached to them. The legislative proposal on NGTs brings some relief by taking the NGTs that fall in category 1 plants out of the GMO regime and making them subject to a much less restrictive set of rules. This deregulation or derogation (a broad exemption from existing rules) would at the same time bring destigmatisation because category 1 products would no longer fall under the GMO legislation. The proponents of the use of NGTs we interviewed therefore consider the NGT proposal to be an important step forward, although they had reservations because the proposal may yet be significantly altered during the negotiations between member states. Various respondents thought the more lenient regime for category 1 NGT products gives breeders in the biotechnological sector room to innovate.[212]

At the same time, some regret that NGTs that do not qualify for category 1 NGT status will remain under the GMO regime. They feel that the relaxed authorisation procedure for category 2 NGT products that meet certain sustainability criteria amounts to little, because the member states can still influence the authorisation procedure,[213] leaving a major stumbling block to the approval of category 2 NGT products in place. Various respondents therefore fear that category 2 NGT status, like the current GMO status, is a recipe for standstill. Interviewees expected category 2 NGT applications will not receive funding because of the uncertainty of obtaining approval for use (or the certainty of rejection).[214]

In addition, the legislative process is open-ended as far as destigmatisation goes. Although category 1 NGT products would no longer be labelled as GMOs, the European Commission's legislative proposal still contains a labelling obligation for source material,[215] in combination with a publicly accessible database in which all category 1 NGT crops must be listed.[216] This would give breeders, including those in the organic sector, the possibility of avoiding NGT products and providing a certain degree of transparency to the public. However, the European Parliament has amended the legislative proposal to include a labelling obligation for category 1 NGT products, for the benefit of consumers. It remains to be seen what happens to this labelling

[211] Interview with plant breeding researcher, WUR; interview with senior advisor for gene technology and biological safety, RIVM.
[212] Inter alia, interview with project manager and programme director, hollandbio; interview with plant breeding researcher, WUR.
[213] Interview with programme director, hollandbio; interview with plant breeding researcher, WUR.
[214] Inter alia, interview with plant breeding researcher, WUR.
[215] Art. 10 COM(2023) 411 final stipulates that this source material must bear the label 'category 1 NGT' plus an identification number.
[216] Art. 9 COM(2023) 411 final.

obligation for end-products in the negotiations between member states. If it remains in place, the question is whether a category 1 NGT label for consumers could avoid the stigmatising effect attached to GMOs.

This will probably depend in part on whether opponents of category 1 NGT products will actively try to stigmatise the consumer label, as happened with GMOs. But one respondent also pointed to the part played by the business community, which he asserts is too fearful of labelling. He believes the labels can also be used as an approval mark, such as the organic label for organic products. In his view, an NGT label stands for sustainability, because the use of cisgenesis and other NGTs makes it possible to considerably reduce the use of pesticides. For category 2 NGT this is explicitly included the sustainability criteria. In this way, an NGT label can be seen as proof that a product contains fewer pesticide residues than commonly found in conventional products. In principle, it is not possible for a herbicide-resistant crop to be approved as a category 2 NGT crop.[217]

5.3.3 Clarity and future-proofing

The interviews reveal that clarity is very important. The need for clarity has both a temporal and a substantive dimension. On the temporal dimension, many respondents pointed out that for a long time it has been known that the legal status of cisgenesis and other NGTs is going to change, but not exactly what will change, or indeed how long it will be before there will be any clarity. This long period of uncertainty is holding up innovation, while competitors outside Europe are forging ahead.[218] Neither will opponents of NGTs necessarily benefit if this uncertainty persists, even if it does mean delaying relaxation of the rules. As the director of Odin remarked in connection with the protracted negotiations between member states:

> A lack of clarity keeps everyone trapped to a certain extent.... It's just exasperating.... Look, I'm glad it's not going ahead, but as long as it's not clear what's happening, you have to stay alert, react, make an effort, and that means less time for other things you could be doing.... You could have spent all that time working on solid solutions to all the issues out there, but now you're just busy with objections.[219]

Respondents also mentioned the sluggishness of the EU legislative process as a problem that drains the ability to respond promptly to future developments. One respondent even felt we would be lucky if the rules were amended once every 10 or 20 years. Any quicker is just not possible in the EU system, he believes.[220]

But there is a widespread desire for the regulatory framework to be revised more frequently to minimise the period of legal uncertainty due to outdated rules and not knowing what the new rules will be. In the interviews on cisgenesis in agriculture, some time was devoted to how experimental and temporary legislation could help, but these options were not discussed in any detail as the legislative proposal on NGTs provided little to go on. In contrast to the proposed EU legislation for medicines discussed in Chapter 6, the NGT proposal does not contain any

[217] Interview with team leader, applied ecology, WUR.
[218] Interview with member of ScL COGEM; interview with senior advisor on gene technology and biological safety, RIVM.
[219] Interview with director of Odin.
[220] Interview plant breeding researcher, WUR.

concrete provisions for experimental rules. It does contain a few temporary elements, but it is doubtful whether these will help to make revision of the rules any easier. The opposite is more likely. We return to this in § 5.3.4, where the most promising option for speeding up the revision of rules will be discussed: delegation.

The substantive dimension of the need for clarity came up in the interviews in relation to the wording of the legislation. As mentioned above, proponents of the use of NGTs were pleased with the flexible regime for category 1 NGT products and thought that breeders could operate within the criteria of equivalence for category 1 NGT. At the same time, though, several respondents felt it was still not clear enough what is and what is not covered by the maximum of 20 genetic changes.[221] This is therefore a potential source of new grey areas. It is noteworthy that the number 20 was mentioned several times in the interviews, but did not always refer to the same thing. In the annex to the original legislative proposal by the European Commission containing the criteria of equivalence for category 1 NGT plants, the number appears twice. The first time it refers to a maximum of 20 genetic modifications 'of the types referred to in points 1 to 5, in any DNA sequence sharing sequence similarity with the targeted site that can be predicted by bioinformatic tools.' One of the types of modification, under point 1, is then defined as 'substitution or insertion of no more than 20 nucleotides.' Both 20s are related, but how this relationship should be understood cannot be conclusively inferred from the text of the annex. Does it mean that a modification, being a substitution or insertion of maximum 20 nucleotides (point 1), may be carried out a maximum of 20 times (preamble), resulting in the substitution or insertion of in total 20 x 20 = 400 nucleotides? This interpretation seems the most logical, but at the same time it seems to provide more leeway than many of the interviewees thought.

Amendments by the European Parliament scrapping the maximum of 20 genetic modifications from the preamble have probably introduced more clarity. This leaves just the maximum of 20 nucleotides, to which the European Parliament has introduced a few exceptions.[222]

Other questions thrown up by the interviews were: Do spontaneous modifications also count? And do modifications have to be added up if there is 'gene stacking'? One respondent gave an example of stacking:

> Say I have a variety in which I've changed 15 nucleotides in two different genes. OK, so that variety has been on the market for two years, no problem. But now I want to add a resistance gene to it, because I have mildew and it's becoming a problem. I've got a resistance gene, which is already in the genome, but I've just got to change a few nucleotides.... But those two different changes, with two years between them, amount to 25 nucleotides. Is this crop permitted or not? ... Or I have one I'm going to cross with another one that I've already modified with 16, and then I'm suddenly up to 35.[223]

[221] Inter alia, interview with member of ScL COGEM; interview with project manager and programme director, hollandbio.
[222] European Parliament legislative resolution of 24 April 2024 on the proposal for a regulation of the European Parliament and of the Council on plants obtained by certain new genomic techniques and their food and feed, and amending Regulation (EU) 2017/625 (COM(2023)0411 – C9-0238/2023 – 2023/0226(COD)).
[223] Interview with member of ScL COGEM.

A question of specific importance for this case study is how the criteria of equivalence relate to cisgenesis. Some respondents thought that cisgenesis by definition falls within category 1 NGT,[224] but that interpretation was refuted by other respondents.[225] This difference of opinion may be connected with the different stages the legislative proposal has already been through. In the original European Commission proposal, cisgenesis was not linked in advance to category 1 NGT or category 2 NGT, which meant that a product of cisgenesis could fall in either category, depending on the specific characteristics of the cisgenesis. In the interviews this led to the question of whether 'one cisgenesis' (in other words, the complete package of modifications, as used in the DuRPh project to insert multiple R genes into a cultivated potato variety) is equal to one modification as described in the preamble to Annex I. A further question in relation to this is which of the five types of modifications mentioned in points 1 to 5 best fits cisgenesis. At first sight, cisgenesis seems to fit into a number of types depending on the specific modifications made. However, points 3, 4 and 5 involve 'targeted' modifications, which would appear to exclude older forms of cisgenesis, as used in the DuRPh project, which are clearly not the type of changes described by the term 'targeted'.[226]

The Dutch government[227] and the European Parliament have drawn attention to this problem, and the European Parliament has amended the proposal by replacing points 2 to 5 with a point 1a, which specifically leaves room for cisgenesis. [228] Point 1a includes the criteria 'insertion of continuous DNA sequences existing in the gene pool for breeding purposes' and 'substitution of endogenous DNA sequences with continuous DNA sequences existing in the gene pool for breeding purposes,' with the term 'targeted' scrapped. The current situation is therefore that the older forms of cisgenesis are highly likely to meet the criteria of equivalence for category 1 NGT plants, as long as they meet the requirement of no more than 20 nucleotides in point 1. It remains to be seen whether the member states will agree to these amendments by the European Parliament.

5.3.4 Delegation and depoliticisation

Various respondents mentioned an important instrument in the legislative proposal on NGTs for amending EU legislation in line with new technological developments more quickly than is now possible.[229] Article 5(3) of the legislative proposal gives the European Commission the power to adapt the criteria of equivalence for category 1 NGT plants in Annex I where necessary:

> The Commission is empowered to adopt delegated acts in accordance with Article 26 amending the criteria of equivalence of NGT plants to conventional plants laid down in Annex I in order to adapt them to scientific and technological progress as regards the types and extent of modifications which can occur naturally or through conventional breeding.

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[224] Interview with plant breeding researcher, WUR; interview with team leader, applied ecology, WUR.
[225] Inter alia, senior policy officer for biotechnology, LVVN.
[226] For this reason, the senior policy officer for biotechnology at LVVN was inclined to classify cisgenesis separately from NGTs, despite the fact that in the NGT legislative proposal cisgenesis is explicitly acknowledged to be an NGT.
[227] See 'BNC document' *Verordening Nieuwe Genomische Technieken* (Regulation on New Genomic Techniques), p. 8.
[228] European Parliament legislative resolution of 24 April 2024 on the NGT proposal (C9-0238/2023).
[229] Interview with policy officer, Plantum; interview with senior policy officer for biotechnology, LVVN; interview with policy officer A, IenW.

This form of delegation considerably increases the adaptivity of the legislation. A key question is how much influence the member states will have on amendments the Commission wants to make in future. The scope of the Commission's delegated powers to adapt the criteria for category 1 NGT plants is defined in Article 26 of the proposal. This does not give the Commission a completely free hand, which is welcome from the democratic legitimacy point of view. The Commission has to consult experts designated by each member state before adopting a 'delegated act'. Moreover, the Commission's delegated powers may be revoked at any time by the European Parliament or by the Council (in which the member states are represented). If not, the Commission's powers are extended for a further period of five years. In addition, the European Parliament or the Council can object to and prevent the Commission's delegated acts.

However, it would seem from the wording of Article 26 that both the revoking of the delegated powers and prevention of the acts amending the criteria for category 1 NGT plants require a majority in the European Parliament or the Council, meaning that vetoes by individual member states or obstruction by a small group of member states would not be enough. This would seem to be a way of avoiding politically motivated tactics for delaying or obstructing amendment of the criteria for category 1 NGT plants. One remaining question is whether during negotiations on the NGT legislative proposal the member states will agree to this delegation of powers to the Commission.

5.3.5 Support and innovation despite limitations

The importance of garnering support for the regulation of cisgenesis and other NGTs came up in various interviews. From the history of the relationship between GMOs and society, multiple respondents noted that the success of NGTs stands or falls on having sufficient public acceptance and taking public concerns seriously.[230] As we saw in § 5.1.2, this was also an important component of the DuRPh project. it was also pointed out that the legacy of social bias against GMOs is still alive,[231] and so obtaining sufficient public acceptance of NGTs may be considered to be an uphill battle.

In this context, the importance of involving all relevant stakeholders, and not just the users of NGTs, in the evaluation of new regulations was stressed. One IenW policy officer added that public support is indispensable.[232]

It is striking that a number of interviewees were less convinced of the dependence of innovation on flexible regulations. Some respondents stated that innovation is also possible under the current regulatory regime. Relaxing the regulations would create more room for innovation, but the legislative proposal for NGTs provides little additional room.[233] One respondent suggested that the limitations in the proposal for category 2 NGT could turn out to be an advantage:

> That not all technology is permitted at the moment, category 1 NGT, may also be an advantage. You could say, let's just get by with the limitations for a few years, see how society reacts, and

[230] Interview with team leader, applied ecology, WUR.
[231] Interview policy officer and director of Plantum.
[232] Interview with policy officer A, IenW.
[233] Interview with plant breeding researcher, WUR; interview with project manager and programme director, Hollandbio; interview with member ScL COGEM.

> then you'll have an idea how to make the next round of changes.... The only thing you can hope to achieve with the new proposals is that in ten-years' time there should be an evaluation of how it has worked out, if it was too strict or not strict enough.[234]

This raises an interesting thought, that innovation does not always takes place despite restrictive regulation, but also sometimes because of it. It is highly questionable whether breeders would have gone ahead with cisgenesis if transgenesis had not been subject to severe restrictions in the EU. Cisgenesis might then never have existed and the innovation pathway would have gone straight from transgenesis to site-directed mutagenesis.

5.4 Concluding remarks

This chapter explored the nature of grey areas in the regulation of cisgenesis in agriculture. Various solution strategies for addressing these grey areas were then discussed with reference to the legislative proposal on NGTs, such as reducing technology specificity, derogation from the existing legislation, and delegation of powers to a regulatory authority such as the European Commission. The need for legal clarity expressed by respondents from different backgrounds was also discussed. These avenues are explored in Chapter 7 in the light of the theoretical reflection on building blocks for robust regulation.

[234] Interview with plant breeding researcher, WUR.

6 Grey areas in red biotechnology: new vaccine technologies

6.1 Background

6.1.1 The context of the Covid-19 pandemic

New vaccine technologies have undergone rapid development over the past five years.[235] This relatively fast development has taken place against the background of the pandemic caused by the SARS-CoV-2 virus (Covid-19), which spread around the world from the end of 2019. In addition to the many measures taken to prevent further infection, efforts were made to develop coronavirus vaccines. However, a particularly challenging problem was that developing conventional vaccines is a complex, time-consuming and costly business. It can take more than ten years before a stable vaccine can be taken to market. In the fight against Covid-19 there simply was not enough time. A quick and effective method was needed to protect the global population. In response, the pace of development of new vaccine technologies, such as vector vaccines and mRNA vaccines, moved up several gears. To make all this legal, the required environmental risk assessment of clinical trials of Covid-19 vaccines based on GMOs was temporarily suspended. This temporary lifting of the need to obtain authorisation was made lawful in EU Regulation 2020/1043.[236] The underlying motive was that this would save time. The Dutch proposal to speed up the authorisation procedure within the existing legislation was not adopted.[237] This temporary suspension has now been lifted.[238]

The various vaccines that were developed work in different ways. In vector vaccines, the DNA or RNA containing the genetic code of the immunogenic protein of the pathogen is inserted into a delivery system (the vector), which is usually a replication-deficient virus.[239] The vector enters the host cell, releases the DNA or RNA with the genetic code of the immunogenic protein and the code is transcribed in the cell. The cell makes the protein and the body then makes antibodies in response to it. The mRNA vaccines have a different modus operandi. No DNA is inserted into a virus and no use is made of a (stripped-down) virus vector. Instead, an mRNA containing the genetic code for an immunogenic protein is delivered into the cytoplasm of the host cell. The mRNA is packaged into lipid nano particles (LNPs). Again, the cell transcribes the genetic code, makes the protein and the body then produces antibodies in response.

Both vector vaccines and mRNA vaccines had previously been used against cancer. The mRNA vaccines have so far proved to be the most successful against some types of cancer.[240] Patients are vaccinated with mRNA containing the genetic code for tumour-specific proteins, the body transcribes the code and makes the protein, which elicits an immune response that clears up the tumour cells.[241]

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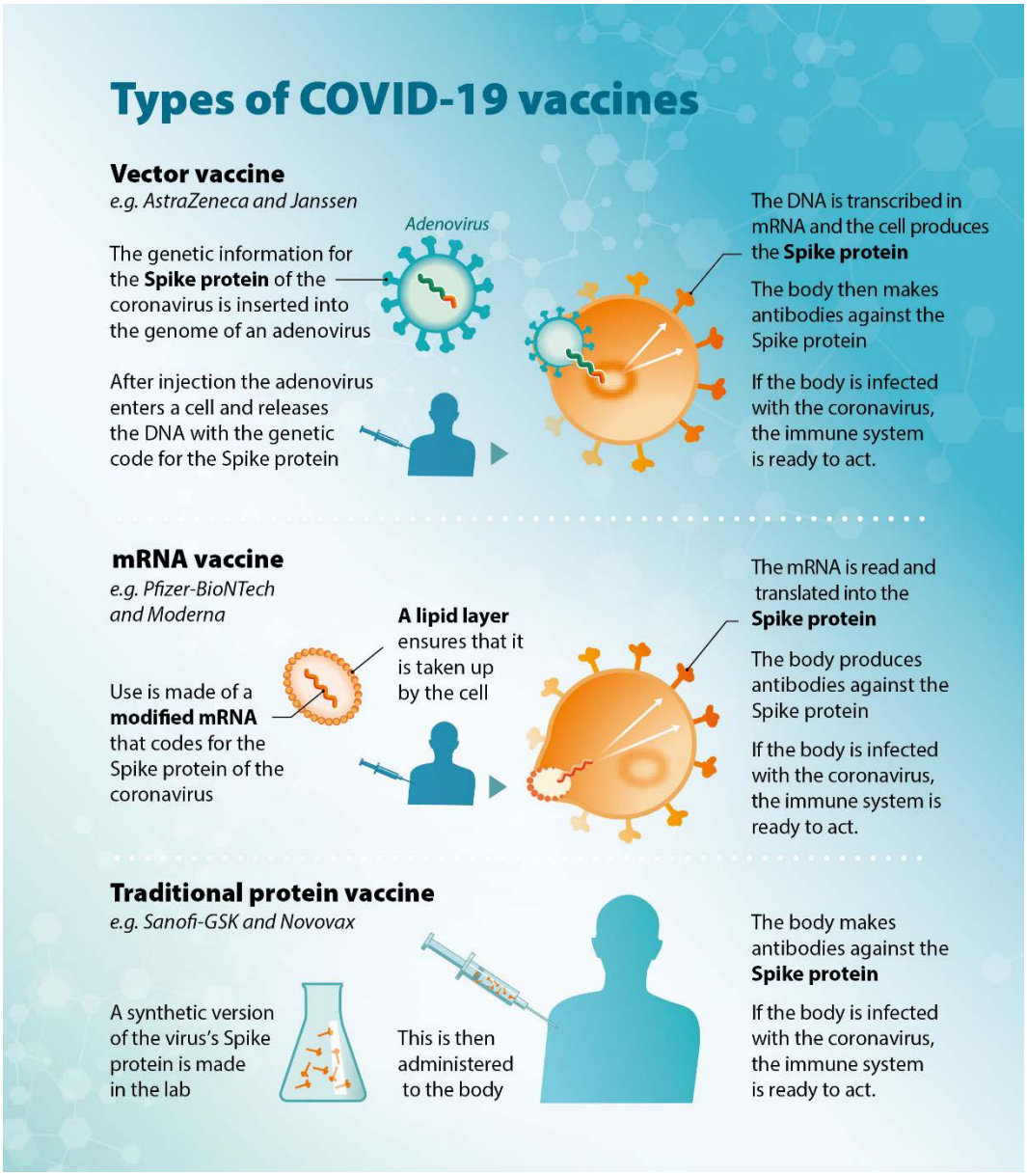
[235] COGEM & Gezondheidsraad, 2023, p. 43.
[236] Regulation 2020/1043.
[237] Poort & Kortleven, 2021; Le Blansch et al., 2022.
[238] *Besluit van 3 mei 2024 tot vaststelling van het tijdstip van inwerkingtreding van artikel III van het Besluit van 20 oktober 2022 tot wijziging van het Besluit genetisch gemodificeerde organismen milieubeheer 2013 (uitvoering verordeningen (EU) 2019/1381 en (EU) 2020/1043)* (Stb. 2022, 407).
[239] COGEM & Gezondheidsraad, 2023, p. 44; Paston et al., 2021.
[240] Bidram et al., 2021; Steenhuysen & Erman, 2022.
[241] Interview with chair of the Netherlands Society of Gene and Cell Therapy (NVCGT).

The mRNA vaccines in particular are good at tackling viral infections such as Covid-19, because so far they have been no less effective than conventional vaccines, are easy to adapt to new variants of the Covid-19 virus and are relatively cheap to make.[242]

In addition, they are not considered to be organisms and so do not fall under the GMO legislation.

Figure 6.1 Overview of Covid-19 vaccines[243]



[242] COGEM & Gezondheidsraad, 2023, p. 42–45.
[243] Taken from COGEM & Gezondheidsraad, 2023.

6.1.2 Two variants of mRNA vaccines

There are two variants of mRNA vaccines: standard mRNA vaccines as described above and self-amplifying mRNA vaccines (samRNA vaccines) (see Figure 6.2). In the latter variant, the samRNA can replicate itself within the cell, which makes the question of the scope of the GMO legislation less clear cut. Just like standard mRNA vaccines, samRNA vaccines contain the genetic code for the immunogenic protein of a pathogen, but also the code for a protein complex from a virus which enables the mRNA to replicate in the cell. This induces a longer immune response and allows a more powerful vaccine to be made with less mRNA.

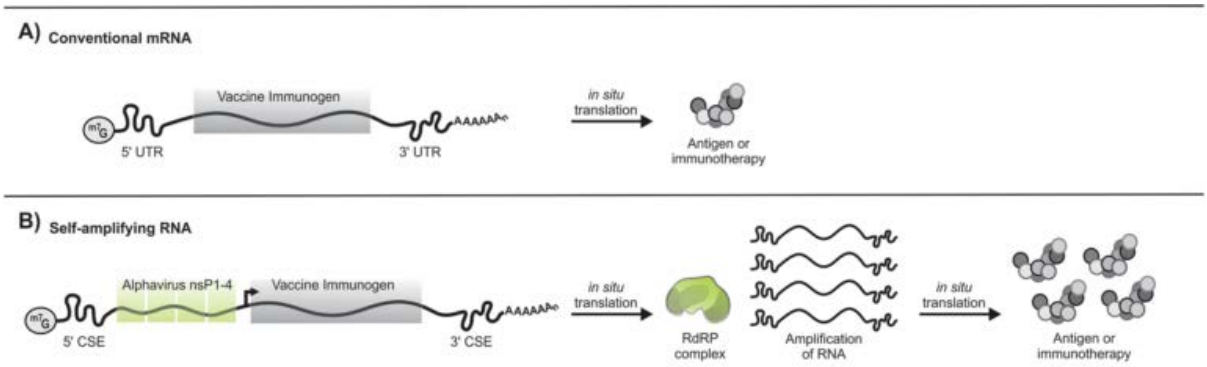
SamRNA vaccines are made by combining the mRNA for the desired immunogen and protective protein with an RNA that codes for viral proteins that can replicate the samRNA. The code for the structural proteins (to make new virus particles) is removed and replaced with the code for the desired immunogenic protein. Because the code for the structural proteins is removed, the samRNAs can no longer make new virus particles.

Just like standard mRNA vaccines, samRNA vaccines can be packaged in LNPs, but also in viral replicon particles (VRPs). VRPs are obtained by providing the missing code for the structural proteins individually on separate mRNA fragments during the production process. These separate mRNA fragments are not inserted into the VRP and because the code is not present on the samRNA itself, the samRNA can replicate itself in the cell but it cannot form new virus particles.[244]

SamRNA vaccines have not yet been made available on the Dutch market, but it is expected they will in future.[245] Production and stability are still major challenges. Also, in contrast to standard mRNA vaccines, they are more difficult to adapt.[246] A few samRNA vaccines have been placed on the market elsewhere in the world: vaccines for Covid-19 have been approved in Japan and India,[247] and in the US samRNA vaccines have been used in pigs against a viral form of diarrhoea[248] and as emergency vaccines for Avian influenza.[249]

[244] See COGEM, 2022; Van der Meulen & Rüdelsheim, 2022. Another name for samRNAs is viral replicons.
[245] Comes et al., 2023, p. 1417 – 1429; the Committee for Medicinal Products for Human Use (CHMP) of the EMA made a positive recommendation on a Covid-19 vaccine based on samRNA, EMA/392588/2024 Kostaive | European Medicines Agency (EMA). The European Commission still has to officially approve this vaccine, but it is expected that the vaccine will be on the market very soon.
[246] COGEM & Gezondheidsraad, 2023, p. 42.
[247] Interview with member of the Subcommittee on Medical and Veterinary Aspects (ScMV) COGEM. Terms such as viral vectors, recombinant viral vectors and recombinant viruses are used interchangeably. Replicons are derived from recombinant viral vectors and are also referred to as stripped-down or defective viruses.
[248] www.biotechnologie.nl/nieuw-mrna-vaccin-vermenigvuldigt-zichzelf/ (last accessed on 27-01-2025)
[249] Interview with senior project leader, molecular virology, BSO and associate director global regulatory affairs, MSD Animal Health.

Figure 6.2 Schematic representation of mRNA and samRNA[250]



In this study we focus on the samRNA vaccines in which the samRNA can replicate itself in a host cell. As one of the respondents said, the last word has not yet been said on the definition of a samRNA vaccine.[251] Different names for samRNAs are sometimes used interchangeably, such as replicons or recombinant viral vectors.[252] Some people consider samRNA to be an mRNA vaccine 2.0; others say it is a stripped-down virus. Also, a distinction is not always made between samRNA vaccines and VRP vaccines (a form of samRNA vaccine). VRP vaccines can be seen as a specific application of samRNA vaccines.[253] All this makes the discussion more complicated.

These differences in the definition of samRNA makes the legal status of these vaccines uncertain, creating a grey area of the scope of the GMO legislation.[254] Do samRNA vaccines, like standard mRNA vaccines, fall outside the scope of the GMO legislation, or does the code for the protein complex and other elements from a virus that enables replication of the mRNA make a difference? And what part does the packaging method play in determining GMO status? COGEM is currently of the opinion that such self-replicating mRNA vaccines fall within the scope of the legislation, regardless of the packaging.[255]

In the following section we explore and analyse the complexity involved in determining the legal status of samRNA vaccines. The legal framework is based on the same principle as the GMO legislation for clinical trials (Directive 2001/18/EC Part B). Some interviewees also referred to the authorisation procedure for contained use (Directive 2009/41/EC) for cases where the vaccine is still in the experimental stage, or to make a comparison with other authorisation procedures.

[250] Taken from Bloom et al., 2021.
[251] Interview with member ScMV COGEM.
[252] Idem.
[253] Hick et al., 2024.
[254] Here too we adhere as far as possible to the terminology used in the Trend Analysis or the terminology used by COGEM.
[255] COGEM, 2024.

6.2 Problem analysis

6.2.1 The ability to replicate: a definition problem

As mentioned above, samRNA vaccines are a further development of mRNA vaccines. The standard mRNA vaccines do not fall under the GMO legislation because they are not derived from an organism. An mRNA is not a biological entity with the ability to replicate. The source material for this type of vaccine does not meet the definition of a genetically modified organism and therefore the vaccines do not fall within the scope of the GMO legislation. The statutory definition of an organism and genetically modified organism is stated in Article 2 of Directive 2001/18/EC:

> 1. 'organism' means any biological entity capable of replication or of transferring genetic material;
> 2. 'genetically modified organism (GMO)' means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

The samRNA vaccines are in a grey area because in addition to the genetic code for the immunogenic protein of the pathogen they also contain the genetic code for the protein complex for replicating the mRNA within the cell, along with other viral elements necessary for replicating the mRNA. This protein complex is derived from a virus, which is the first stumbling block. Does the viral protein complex make a samRNA vaccine an organism as defined in Article 2(1) of Directive 2001/18/EC? Directive 2009/41/EC includes viruses in its definition of a microorganism, but mRNA is not considered to be an organism. The situation is made more complex when interpreting the term 'ability to replicate'. What does this mean? 'Replicate' can be understood to mean 'copy' or 'duplicate'. In samRNA vaccines the mRNA can make a copy of itself within the cell, but not produce any new virus particles that can then infect another cell.

The definition of an organism as a biological entity with the ability to reproduce offspring raises questions concerning the use of samRNA vaccines. Is it sufficient that Directive 2009/41/EC states that a virus is an organism, or is the ability to replicate the decisive factor? And which replicable elements matter: duplication of the RNA within the cell, forming new virus particles or spreading? A biological and environmental safety officer at Biosafety Support referred to the biological definition of an organism in which the emphasis is on the ability to sustain itself. If no new virus particles are formed, it cannot sustain itself and is therefore not an organism. A professor of tumour virology at University Medical Center Groningen (UMCG) stated that the RNA of a VRP or samRNA is only detectable in the body for a few days. One respondent commented that the ability to reproduce independently is indeed a feature of an organism, but that in the GMO legislation this is somewhat of a semantic issue. Viruses need a host cell to be able to reproduce, but at the same time they fall within the scope of the GMO legislation.[256]

In theory, a samRNA inside a cell can recombine with the RNA of a wild-type virus that is present within the cell at the same time.[257] If that happens, though, can new virus particles spread outside the cell, or are they unable to survive outside the cell? And how important is this? According to COGEM, adenoviral, lentiviral and retroviral vectors cannot form new virus

[256] Interview with chair of NVCGT.
[257] Hick et al., 2024. p. 2521.

particles and cannot replicate, even within a cell, but they do fall within the scope of the GMO legislation.[258]

In this debate, various terms overlap and are sometimes used interchangeably. The distinctions between terms can be legally relevant: copy, duplicate, replicate and spread. When a virus infects a cell, it acts as follows: the viral genome (in this case, RNA) of the virus duplicates or copies itself inside the cell, forms new virus particles and then spreads to other cells. Is *replication* the whole process of *duplicating* genetic material within a cell and forming new virus particles which then *spread* to other cells, or is just one of these stages enough? Opinions are divided. Some respondents consider only the whole process of forming and spreading of new virus particles to be replication.[259]

6.2.2 Packaging and delivery VRPs versus LNPs

A second significant stumbling block in the semantic discussion about the definition of an organism and a GMO concerns the method of packaging and delivery. As discussed in the background section, standard mRNA vaccines are packaged in minuscule fat globules called lipid nano particles (LNPs). These lipid particles are not biological entities and are produced synthetically. In addition, the particles are broken down or shed after they have completed their task. This packaging method can also be used for samRNA vaccines, but they can also be packaged in VRPs.

The GMO status of VRPs is also disputed. A biological safety officer at Biosafety Support is adamant that that they are not GMOs, because VRPs are derived from viruses but cannot form new virus particles. Nevertheless, in the Netherlands they are currently taken to be GMOs.

In a recent statement on the GMO status of VRPs, the European Commission pursues a different line of reasoning.[260] The Commission argues that VRPs are not GMOs because they can no longer form virus particles. This seems to equate replication with the formation of new virus particles. In this statement, the addition of the legal definition 'ability to replicate' is decisive for the determination of their GMO status. However, VRPs are made using a recombinant technique and not by genetic modification. The replicon system is made by genetic modification,[261] which makes the legal GMO status of samRNA vaccines packaged in VRPs even more complex.

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[258] COGEM, 2024.

[259] Interview with biological safety officer (BSO) and environmental safety officer, Biosafety Support; interview with professor of tumour virology, UMCG; interview with senior project leader, molecular virology, BSO; interview with associate director global regulatory affairs, MSD Animal Health. In this study we use neutral terminology such as copy or duplicate as far as possible. A virus only duplicates itself in the cell. It can go through the entire process (up to and including the formation of new virus particles, which are then shed from the cell) or only part of it (e.g. only the duplication of the RNA genome).

[260] COGEM, 2024.

[261] Interview with senior project leader, molecular virology, MSD Animal Health; interview with BSO, MSD Animal Health; interview with associate director global regulatory affairs, MSD Animal Health.

COGEM is critical of the Commission's statement and points out the inconsistencies in it.[262] COGEM is of the opinion that VRPs should be classified as GMOs, saying 'a VRP is an entity, something that has a real existence, and can by definition replicate'.[263] COGEM points to the proteins and other viral elements that enable the modified viral genome to replicate inside the host cell. Moreover, there is a 'transfer of genetic material'. 'VRPs consist of genetic material and the infection of the host cells involves the insertion of the viral genome, which is used to express transgenes in these host cells.'[264]

This highlights the fact that the European Commission's definition of replication is different from COGEM's definition. The Commission defines replication as making new virus particles and stresses their spreading outside the cell. COGEM uses a broader definition and distinguishes between two types of replication: 1) replication of the mRNA/DNA, and 2) replication of virus particles. An initial analysis therefore reveals a difference of opinion about replication in which terms like copying, duplicating and producing virus particles are interpreted differently.

In its advice on this statement, COGEM also points to inconsistencies in the reasoning about the GMO status of modified viruses within the EU legislative framework. According to Directive 2009/41/EC, viruses are organisms; the ability to replicate new virus particles is of secondary importance. Viroids and some replication-deficient viral vectors can no longer make new virus particles, but in line with Directive 2001/18/EC they are still considered to be organisms, and therefore GMOs. COGEM argues that if we were to follow the Commission's line of reasoning, these viroids and replication-deficient viral vectors should also not be GMOs. But they do fall within the scope of the GMO legislation.

6.2.3 The consequences of the GMO status of samRNA vaccines

The two stumbling blocks mentioned above concern the definition of an organism and the debate about the GMO status of a stripped-down virus. This clearly reveals the shortcomings of the current legal framework in relation to rapid technological developments. The current definitions are creaking at the seams and are leading to ever more grey areas instead of providing clear definitions.

In the following analysis, we package these stumbling blocks together and focus on the different interpretations of the ability to replicate and the definition of an organism. We also analyse the differences in the conclusions that can be drawn from this. The debate about VRPs plays a large part in this analysis, because the various arguments for the GMO status of VRPs are also relevant to the GMO status of samRNA vaccines.

There appears to be a difference of opinion about the ability of samRNA vaccines to make copies of their RNA within a cell.[265] The presence of the structural protein complex and other

[262] On this point, we see differences between the Netherlands and the European Commission, but also between other member states. An additional complexity is that samRNA vaccines are considered to be GMOs for contained use and deliberate release, but not for marketing authorisation (as evidenced by the CHMP advice on the samRNA vaccine Kostaive. See EMA/392588/2024 https://www.ema.europa.eu/en/medicines/human/EPAR/kostaive.
[263] COGEM, 2024.
[264] COGEM, 2024.
[265] De Schrijver, Wijns & Rüdelsheim, 2024.

viral elements necessary to enable duplication of the mRNA in the cell is even a distinctive feature of samRNA vaccines compared with 'standard' mRNA vaccines.

The debate seems to be centred primarily around whether duplication of RNA within the cell should be seen as replication and therefore as meeting the definition of a GMO. However, this is a simplification of the scientific and legal debate. The distinction between 'duplicating' or 'copying' a single mRNA and 'forming VRPs that can spread outside the cell' appears to be decisive. In the interviews. this distinction was emphasised by various respondents.[266] However, they did not relate this to a narrow or broad interpretation of 'replication', but to the safety aspect.

Several respondents who work on or have experience with the development of samRNA vaccines, similar vaccines or VRPs emphasise that their ability to produce new virus particles has been disabled, eliminating the risk of the virus spreading in the environment (no environmental risk).[267] Nor can new virus particles be formed and spread, which means that these replicon particles should not be regarded as organisms. They cannot survive and persist. One respondent commented that the GMO Office interprets the definition of a GMO to the letter of the law, putting less emphasis on the underlying goal of protecting human and environmental safety. According to this respondent, the *ability to replicate* is relevant to the definition of a GMO insofar as it poses a risk of virus particles spreading further in the environment. She said:

> As far as I'm concerned, replication is linked to spreading because the GMO legislation assumes that GMOs should be contained, and not introduced into the environment.[268]

In this opinion, replication refers to the whole process of copying genetic material, forming new virus particles and spreading to other cells.[269]

Another respondent stressed that in his view the GMO Office is more flexible and willing to explore options with applicants for a more positive interpretation within the framework of the law; in other words, it offers more scope for interpretation.[270] A senior advisor on gene technology and biological safety at RIVM said they were bound by the law, including the purpose of the legislation.

According to Hicks et al. (2024), on paper there is a risk that the virus particle in the host cell will recombine with a wild-type virus that happens to be in the cell at the same time. It would then be able to spread outside the cell. However, research into the risks of recombination between a specific samRNA vaccine and the mRNA of a wild-type alpha virus shows that this risk is small, say the authors. Replication remains limited within the cell.[271] The reasoning that seems to follow from this is that there is no environmental risk, because these particles are unable to replicate (in the broad sense of the word). Some respondents conclude from this that the lack of

[266] Interview with chair of NVCG; interview with BSO, Biosafety Support; interview with professor of tumour virology, UMCG; interview with senior project leader, molecular virology, MSD Animal Health.
[267] Interview with member ScMV COGEM; interview with BSO, Biosafety Support; interview with professor of tumour virology, UMCG.
[268] Interview with BSO, Biosafety Support.
[269] Idem.
[270] Interview with chair of NVCGT.
[271] Hick et al., 2024.

an ability to replicate means that these particles are not organisms. Other respondents suggested that at the very least the environmental risk assessment is unnecessary if it has been established that these vaccines are safe and should therefore not fall under the GMO legislation.[272]

A senior advisor on gene technology and biological safety at RIVM said about this:

> The red biotech community in general does not dispute the need for a thorough environmental risk assessment. Only, what I do sometimes see is that when the outcome of the environmental risk assessment is 'it's safe', which is very often the case, people then think that the whole assessment isn't necessary. And then we're back to that first aspect of the legislation, that the assessment, as part of the decision-making process, is thought to be an inhibitory factor.[273]

In his opinion, the question of whether something is a GMO has nothing to do with whether it is safe or not. This can only be assessed once the environmental risk assessment has been carried out. He reiterates the purpose of the GMO legislation: to ensure human and environmental safety. If the GMO legislation has to be observed, each GMO must be subject to an environmental risk assessment irrespective of whether the outcome is known in advance. This is in line with the precautionary principle underlying the GMO legislation. If the environmental risks are insignificant, this does not mean it is not a GMO, but that it can be authorised. Any exemption from the authorisation requirement for certain applications can be regulated by law, but as long as that is not the case, the law should be observed.

And that brings us back to the legal definition of an organism and a GMO.

Not all respondents disputed the GMO status of samRNA vaccines. Various respondents stressed the importance of the environmental risk assessment because it is impossible to make generic claims about the safety of a technology.[274] Some respondents therefore felt that simply releasing a technology for use is not desirable as it could be used incorrectly or for improper purposes. It is the government's task to protect society against such risks.[275] However, they do dispute the value of the environmental risk assessment for VRPs, samRNA vaccines and similar vaccines under the current procedures. One respondent said that having to repeatedly apply for a permit to carry out clinical trials on the same VRP was superfluous. If they are considered to be safe, going through the same application process is a pointless exercise, because the outcome is already known.[276]

Some respondents questioned what the legal definition of genetic modification actually means.[277] If no DNA is altered, can there be any genetic modification? This would then call into

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[272] Interview with BSO, Biosafety Support; interview with professor of tumour virology, UMCG; interview with senior project leader, molecular virology, BSO and associate director global regulatory affairs, MSD Animal Health.
[273] Interview with senior advisor on gene technology and biological safety, RIVM.
[274] Interview with chair of NVCGT; interview with member ScMV COGEM; interview with senior project leader, molecular virology; interview with BSO, MSD Animal Health; interview with associate director global regulatory affairs, MSD Animal Health; interview with professor of tumour virology, UMCG.
[275] Interview with chair of NVCGT; interview with member ScMV COGEM.
[276] Interview with senior project leader, molecular virology, MSD Animal Health.
[277] Interview with member ScMV COGEM.

question the definition of a virus: is the genome itself also a virus, or does the virus particle have to be 'a whole'?

Various respondents raised the impediment of a 'GMO label'. In some cases, the 'GMO label' and the GMO authorisation process for contained use and for clinical trials can cause delays.[278] Various respondents mentioned the large amounts of data that have to be submitted for the environmental risk assessment, some of which are not always available. One respondent explained:

> We had to think of a method to demonstrate that no replicating virus is created during the production of the vaccine; in other words, to demonstrate that something is not present. Eventually, in consultation with statisticians, we developed an assay that shows that no more than one or two virus particles can be present in each batch.[279]

At the very least, the GMO authorisation procedure throws up additional obstacles whose relevance can in some cases be disputed,[280] and definitely, as described above, when the environmental risk assessment for the use of a certain delivery system or platform has already been carried out (and found to be safe). The environmental risks generally do not change if the same platform is used for other applications. There is a clear desire to abolish such procedures where they lead to delays. For this reason, a few respondents would prefer to see some applications excluded from the GMO legislation.[281] For the cases outlined above, one option could be a simplification of the procedure, while maintaining supervision.[282] A generic downscaling of containment requirements for work with viral replicons derived from alphaviruses and flaviviruses, as proposed by COGEM in 2022, was cited as an example of such an approach.[283]

Most respondents acknowledged the discrepancy between the existing legal framework and technological developments, although one respondent did say that the legal framework works well. This respondent acknowledged the relevance of an environmental risk assessment in addition to the assessment of the health risks of new medicines, gene therapies and vaccines. He feels that while many people found Directive 2001/18/EC to be obstructive and a source of much uncertainty in the initial period after it came into force, the legal framework is now clear and practicable. This respondent pointed to the room for interpretation allowed by some definitions and procedures, which still had to be fully operationalised when they were first introduced. This room for interpretation may also work for future developments.[284] A policy officer for biotechnology safety at the Ministry of Infrastructure and Water Management also

[278] Interview with senior project leader, molecular virology, MSD Animal Health; interview with BSO, MSD Animal Health; interview with associate director global regulatory affairs, MSD Animal Health.
[279] Interview with professor of tumour virology, UMCG. These objections are not specifically aimed at the authorisation procedure for samRNA vaccines, but apply to several types of research with GMOs and indicate that a GMO status can throw up additional obstacles.
[280] Interview with member of COGEM; interview with professor of tumour virology, UMCG.
[281] Interview with senior project leader, molecular virology, MSD Animal Health; interview with BSO, MSD Animal Health; interview with associate director global regulatory affairs, MSD Animal Health.
[282] Interview with senior project leader, molecular virology, MSD Animal Health; interview with BSO, MSD Animal Health; interview with associate director global regulatory affairs, MSD Animal Health.
[283] COGEM, 2022; Van der Meulen & Rüdelsheim, 2022.
[284] Interview with chair of NVCGT.

mentioned this room for interpretation,[285] mentioning that 'safety' is not included in the legal definition, but is a determining factor in the interpretation of 'ability to replicate'. In relation to this, the lack of agreement between member states was also mentioned. In some member states, for example, gene therapy is considered to be contained use, in others it is deliberate release. These differences in interpretation can be resolved through harmonisation, a tighter definition or a specific interpretation.[286]

6.3 Solution strategies

6.3.1 Simplify procedures for contained use

Most respondents who work with samRNA vaccines, VRPs or other replicating mRNA vaccines said they want clear and specific definitions and efficient (and in some cases simplified) procedures.[287] One respondent said the fact that the procedural requirements for applications under the GMO legislation are so much more demanding than for non-GMOs or wild-type viruses leads to much frustration. A recurring theme in the interviews was the process-based versus product-based approach,[288] but this was not thought to be a way forward for fear of an increase in the paperwork for wild-type viruses.

Respondents mentioned several strategies for meeting the need felt among practitioners for both simplified procedures and more clarity. These solutions may not be specifically geared to future-proof regulation, but they do offer ways to remove or reduce the obstacles experienced in the authorisation procedure.

For example, one respondent's advice was to have preliminary discussions with the GMO Office to clear up any ambiguities and speed up the process.[289] Other suggestions were made for simplifying the authorisation procedure for contained use when a delivery system or platform that has already been through an environmental risk assessment is used for other applications. The administrative burdens applicants experience are primarily for laboratory scale I (containment level ML-I) and laboratory scale II (ML-II). The requirements for these classes could possibly be eased or simplified.[290] The current national GMO legislation already has a certain amount of in-built flexibility to do this. Comparisons were made with similar procedural simplifications, such as a generic downscaling of containment requirements, the authorisation procedure with a standard set of licence conditions (VOV) (Art. 3.24 et seq. Genetically Modified Organisms Decree 2013)[291] and the Article 2.8 procedure (Genetically Modified Organisms

[285] Interview with policy officer B, IenW.
[286] Interview with policy officer B, IenW.
[287] Interview with member of COGEM; interview with BSO, Biosafety Support; interview with professor of tumour virology, UMCG; interview with senior project leader, molecular virology, MSD Animal Health; interview with BSO, MSD Animal Health; interview with associate director global regulatory affairs, MSD Animal Health.
[288] Interview with member of COGEM; COGEM, 2019.
[289] Interview with professor of tumour virology, UMCG.
[290] Interview with member of COGEM.
[291] We obtained further information on the background to the VOV from an employee at the Ministry of Infrastructure and Water Management via Marie-Louise Bilgin, member of the supervisory committee.

Decree 2013).[292] These possibilities apply to containment. Another example that was mentioned was the fast-track procedure for clinical trials introduced in the Netherlands at the start of the Covid pandemic.[293] This procedure is for deliberate release.

The introduction of a fast-track procedure or generic downscaling would, however, require amendment of the current national legal framework, but can be regulated in part via annexes and updates (Art. 2.2 Genetically Modified Organisms Decree 2013).

6.3.2 Centralise the authorisation procedure for clinical trials

In anticipation of the proposal for new EU legislation on medicinal products (proposal for a revision of the pharmaceutical legislation), the possibility of combining the environmental risk assessment and the medical ethical review of clinical trials was discussed in some interviews. The environmental risk assessment and the medical ethical review could then be carried out by the Central Committee on Research Involving Human Subjects (CCMO) or similar body. A scientific staff member of the CCMO thought this was an interesting option for further consideration. The CCMO is responsible for reviewing medical research with specific ethical, legal or social issues or research requiring highly specialised expertise. This committee has members representing a wide variety of expertise.[294] The CCMO staff member also mentioned various obstacles standing in the way of this possible dual role for the CCMO.[295] Several respondents also had reservations about this option.[296] The knowledge required to perform a good environmental risk assessment is highly specific and case-dependent, which requires a diversity of scientific expertise.

The CCMO has a wide range of expertise, but not in environmental risk assessment and certainly not for each individual case. COGEM does have this expertise, but at the national level the pool of available experts is not much bigger than this. The CCMO could acquire the additional expertise it needs from COGEM, but this would not really solve the problem.[297] The environmental risk assessment would still have to be done via COGEM. One respondent added that centralisation at the European level may be easier to arrange. The pool of experts in various aspects of environmental risk assessment of GMOs would then be bigger, making it relatively easier to add expertise to the central committee.[298] In the proposal for new EU pharmaceutical legislation, the task of carrying out environmental risk assessments of clinical trials of GM

[292] Art 2.8 Genetically Modified Organisms Decree 2013 permits requests to be made to the minister to lower the containment level when an assigned higher containment level is stricter than necessary. This only concerns contained use.
[293] Interview senior advisor on gene technology and biological safety, RIVM.
[294] The Dutch Medical Research Involving Human Subjects Act (WMO) stipulates that medical scientific research involving human subjects must undergo a review procedure. Research subject to the WMO may be reviewed by the Medical Ethical Review Committee (METC) or by the CCMO. In the Central Review of Medical Research Involving Human Subjects Decree (*Besluit centrale beoordeling medisch-wetenschappelijk onderzoek*) the legislator has assigned the review of specific cases, including gene therapy, to the CCMO.
[295] Interview with scientific staff member, CCMO.
[296] Interview with chair of NVCGT; interview with member of COGEM; interview with policy officer B, IenW.
[297] Interview lid ScMV COGEM.
[298] Idem.

medicinal products for human use is also allocated to a central committee of the European Medicine's Agency (EMA) (see further § 6.3.3).[299]

One respondent commented that there is a certain amount of resistance in Dutch government departments to combining these procedures because the two procedures are currently the responsibility of different ministries (Infrastructure & Water Management and Health, Welfare & Sport).[300]

The proposal for a revision of the EU pharmaceutical legislation makes a distinction between centralisation and harmonisation at different levels: the procedures for contained use and deliberate release remain the responsibility of the member states and national bodies,[301] but are harmonised as far as possible.[302] An exception is made for clinical trials of medicinal products for human use that consist entirely or in part of GMOs. The environmental risk assessment for these trials will probably be carried out by the Committee for Medicinal Products for Human Use (CHMP),[303] but the authorisation procedure for placing on the market is centralised. This procedure has already been centralised at the EU level, but still includes two authorisation procedures under the EU GMO legislation and the EU medicinal products legislation. Under the new pharmaceutical legislation, these procedures would be combined, as described above for the role of the CCMO for the authorisation of clinical trials.

6.3.3 Robustness through centralisation

Centralisation was not only seen as a possible route for simplifying procedures, but was also mentioned in relation to future-proofing the GMO legislation for clinical trials. Several respondents suggested establishing an EU body or committee responsible for decisions to amend annexes or lists of safe techniques.[304] One respondent drew attention to the mandate of the Committee for Advanced Therapy (CAT) to add therapies to the list of safe therapies.[305] The CAT is an EMA committee and is responsible for preparing draft opinions on all applications for advanced therapy medicinal products (ATMPs). The CHMP then decides on the application. In addition, its remit includes making scientific recommendations on the classification of ATMPs and preparing scientific advice on the status of specific ATMPs.[306] A similar scientific committee could be established for classifying (safe) gene techniques. It should be noted that under the revision of the pharmaceutical legislation, if adopted, the CAT would be abolished.[307]

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[299] Art 2 COM (2023) 192 final.
[300] Interview with the chair of NVCGT.
[301] *BNC-fiche Herziening EU farmaceutische wetgeving*; COM (2023) 192 final; COM (2023) 193 final.
[302] Harmonisation is not entirely dependent on the revision of the EU pharmaceutical legislation and is already underway.
[303] See Art. 177 COM (2023) 193 final.
[304] Interview with senior project leader, molecular virology, MSD Animal Health; interview with BSO, MSD Animal Health; interview with associate director global regulatory affairs, MSD Animal Health; interview with senior advisor on gene technology and biological safety, RIVM; interview with scientific staff member, CCMO.
[305] Interview with scientific staff member, CCMO.
[306] https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat (last accessed on 27-1-2025); Regulation 2394/2007.
[307] Artikel 2 COM (2023) 192 final.

One respondent mentioned another possible role for such a centralised body: selection at the gate, in which it would assess whether or not a technique, specific platform or application falls within the scope of Directive 2001/18/EC.[308] This suggestion is in line with the idea of simplifying the procedure for delivery systems or platforms that have already undergone an environmental risk assessment but are now used for a different application (see § 6.3.1). In this context, one respondent argued for starting with a preliminary environmental risk assessment to form the basis for assessing whether or not something should be considered a GMO.[309] This would link the definition of a GMO to the safety aspect.

One respondent had doubts whether such selection at the gate would actually eliminate any barriers.[310] A senior advisor on gene technology and biological safety at RIVM disputed whether the legal framework is the right place for repeatedly changing the list of safe techniques as new developments emerge. Amending the law is a complex and slow process. The flexibility and robustness needed to adapt to new developments without losing sight of the purpose of the law could be found outside the law. This already happens at the national level by means of the VOV procedure of authorisation with standard conditions.

6.3.4 Robustness through evaluation

Robustness can also be achieved by building in periodic evaluations. At the national and EU level, each new piece of legislation is evaluated after a fixed period. Several respondents argued for an evaluation on a more regular basis, for example once every five years. An employee of MSD Animal Health said:

> It would be great if there were a way to make the legislation more flexible or quicker to adapt. If you want to keep Directive 2001/18, it should be brought up to date with the latest technology every five years or so. You would need to set up a committee on 1 January 2025 to do that, and it would start work on 2 January for the 2030 update. It's not a case of waiting until 2030 and then saying 'Oh, I should take a look at that sometime,' but just keeping the legislation up to date. If you look at 2001/18, it's 25 years old. At the time it was very modern, but things move fast, so you have to update this kind of thing every five years. Of course, these technologies have lots of advantages. Considering how many outbreaks of these diseases we have everywhere today, if you want to keep up, if you want to be able to work with the best techniques, the government has to keep the regulations in order.[311]

A policy officer for biotechnology safety at the Ministry of Infrastructure and Water Management endorsed the importance of regular evaluations, adding that the evaluations should include insights and opinions from a diverse range of stakeholders.[312] It is not just the experiences with implementing the legislation and the possible obstacles that are relevant for the evaluation, but also a broader societal perspective. This fits in with a recurrent review at the European level of the interpretation of the legal definition, as discussed above.

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[308] Interview with associate director global regulatory affairs, MSD Animal Health.
[309] Interview with BSO, Biosafety Support.
[310] Interview with chair of NVCGT.
[311] Interview with associate director global regulatory affairs, MSD Animal Health.
[312] Interview with policy officer A, IenW.

6.3.5 Robustness by amending the definition of an organism

In § 6.2 we saw that there is disagreement about the definitions of an organism and a GMO. In addition, various member states take different views on the appropriate containment levels for some applications as either contained use or deliberate release. According to a policy officer at the Ministry of Infrastructure and Water Management, harmonisation will help to resolve these differences of opinion, while a clear definition or concrete interpretation at the EU level can help to prevent grey areas. Under the new EU pharmaceutical legislation, these applications would be deliberate release.[313] But while there is a need for a robust regulatory framework, a clear definition could also be a constraint. This policy officer acknowledged the complexity involved in repeatedly amending the legal definition, but felt that a regular review would be possible, in which the specific interpretations of the definitions would be harmonised at the EU level. Interpretation at the EU level would provide more guidance for interpretating the definitions and provide a framework for action for the member states.

One respondent made concrete suggestions for amending the definition of an organism, proposing to replace 'or' with 'and'.[314] An organism would then be any biological entity capable of replication **and** of transferring genetic material.

This respondent also suggested a different authorisation procedure, focusing on more general values in a concrete case rather than on the definition of an organism and a GMO.[315] This could make the procedure more future-proof because these general values would also be applied to new developments.

6.4 Concluding remarks

The various suggestions proposed by respondents for making the authorisation procedure more efficient and simpler and making the legislative and regulatory framework more future-proof have different implications. Some suggestions could be implemented relatively easily in national laws and regulations, but others would require amendments to EU legislation or would at least push the boundaries of EU legislation.

Chapter 7 contains an analysis of the findings of this case study in the light of theoretical insights on robust and future-proof regulation. The chapter also discusses the (political) feasibility and desirability of these suggestions.

[313] Interview with policy officer B, IenW.
[314] Interview with associate director global regulatory affairs, MSD Animal Health.
[315] Idem.

Part III Towards robust regulation

7 Putting robust regulation into practice

7.1 Introduction

In this chapter, the theoretical analysis in Part I and the case studies in Part II are combined to answer the question 'How can the regulatory regime for GMOs be made *more robust*?' We begin with an analysis of the nature of the grey areas in the case studies, resulting in the identification of the primary needs in practice and how these relate to robust regulation (§ 7.2). We then discuss how the different types of building blocks described in Chapter 3 could help to make the legislation more robust. The role of abstract formulation of legislation is discussed in § 7.3 and the potential contribution of regulatory agencies and lower levels of legislation are discussed in § 7.4. In § 7.5 we consider temporary and experimental legislation, and § 7.6 discusses judicial law-making. In a concluding section (§ 7.7) we draw up the balance. This chapter closes with a table summarising the advantages and disadvantages of the various building blocks identified from our theoretical and empirical research.

7.2 Grey areas in the regulation of green and red biotechnology

7.2.1 Regulatory disconnection as a consequence of GMO status

In both case studies we identified grey areas, or, in the precise terminology of Chapter 2, situations of regulatory disconnection. The grey areas in the green and the red case studies display similarities and differences in their nature and origin. The similarities are that stakeholders in both cases found the existing regulatory regime to be more restrictive and burdensome than they felt was justified by the protection goal of the legislation.[316] This is regulatory disconnection caused by 'over-inclusive regulation'.[317] This form of regulatory disconnection is largely a consequence of the fact that cisgenic crops and samRNA vaccines fall under the definition of a GMO, which means lengthy and costly administrative requirements and hurdles that do not apply to non-GMO crops and non-GMO vaccines. Many of the stakeholders and experts we interviewed said that the characteristics of the crops or vaccines that are classified as GMOs by the legislation do not in themselves pose risks additional to those of non-GMO crops and non-GMO vaccines.

However, it must be emphasised that this form of regulatory disconnection is not primarily a result of regulation that is not adaptive enough to accommodate new technological development, but is the consequence of a deliberate political decision to make specific regulations for different types of genetic modification, for which there also appears to be sufficient public support in Europe. The separate status of GMOs is motivated by the assumption that genetic modification techniques can involve new and unknown risks and therefore should be treated with extra caution. This puts an emphasis on preventing over-permissive regulation; in other words, regulatory disconnection in the form of 'under-inclusive regulation'.[318] If the risk assessment shows that certain GMOs are sufficiently safe, this does not necessarily mean that having to go through the GMO authorisation procedure was unjustified. This view was also held by some of the interviewees. On the other hand, some felt that GMOs deserve a separate status on ethical grounds, because genetic modification techniques

[316] See § 5.3.1 and § 6.2.3.
[317] See § 2.1.
[318] Cf. § 2.1.

interfere with nature more profoundly than conventional techniques. This position came up in our research as well, particularly in discussions about green biotechnology.

The GMO legislation, and specifically the environmental risk assessment, contains burdensome provisions for both cisgenic crops and samRNA vaccines. For cisgenic crops there is also little or no prospect of obtaining marketing authorisation. The DuRPh project has shown that the GMO legislation permits developing cisgenic crops and testing them in field trials, but the influence of obstructive EU member states in the GMO authorisation process makes access to the market impossible or so uncertain that it is economically impractical. This can be seen as a strong from of regulatory disconnection, as this obstruction does not seem to be motivated or justified by the protection goal of the GMO legislation. For GM medicines, which in the Netherlands includes samRNA vaccines, there is no political obstruction of market access. However, these vaccines face not only the administrative hurdle of the GMO environmental risk assessment, but also the medical ethical review.

7.2.2 Regulatory disconnection caused by legal uncertainty

In both case studies, an additional source of regulatory disconnection is legal uncertainty[319] about the application and scope of the GMO status. Both cisgenic crops and samRNA vaccines were developed after the adoption of the legal definition of a GMO, and neither innovation could be unambiguously classified as a GMO or a non-GMO. For cisgenesis, this ambiguity has been resolved; the last reasonable doubt about the GMO status of cisgenic products was dispelled by the decision of the CJEU in case C528/16.[320]

For samRNA vaccines, the legal uncertainty remains, partly as a result of disagreement between stakeholders on the applicability of the legal criterion 'ability to replicate', which is part of the definition of a GMO. Does this criterion refer exclusively to vaccines that can spread outside the host cell, or does it also apply to vaccines that can only copy themselves within the host cell? This distinction is important because spreading outside the cell presents greater safety risks. From the case study it became clear that experts take different views on this.[321]

The scientific debate carries through into disagreement between the European Commission, which does do not consider vaccines based on VRPs to be GMOs because they cannot spread outside the cell, and COGEM and the GMO Office, which reject this interpretation. In addition to this disagreement, the legal uncertainty is compounded by the fact that the Commission's position is not entirely consistent. It considers that other applications that involve the use of replication-deficient viral vectors are GMOs, even though they no longer have the ability spread. Such contradictions raise questions among implementing agencies, researchers and applicants.[322] As an EU body, the European Commission has higher authority. If such

[319] Idem.
[320] See § 5.2.2.
[321] See § 6.2.
[322] A recently published report commissioned by the Ministry of Infrastructure and Water Management sets out the variety of definitions of organisms and GMOs within the EU and discusses the different interpretations of the replication criterion. It points to a degree of consensus that seems to exist on the

differences in interpretation remain, the dispute can be brought to the CJEU, which in specific cases has the final word as legal authority.

The disagreement between the European Commission on one side and COGEM and the GMO Office on the other can lead to legal uncertainties, because the competence to interpret much EU legislation lies both at the EU level and with the member states. This is particularly the case with EU directives, which the member states have to transpose into national legislation.[323] This can sometimes lead to conflicting differences of interpretation between the European Commission and the member states, and between member states. Another example that came up in the red case study is that in some member states gene therapy is considered to be contained use and in other states it is deliberate release.[324] The legal uncertainty that arises from these types of differences can create obstacles because the development, deliberate release and marketing of genetically modified products are usually strictly national matters. Moreover, differences between countries can throw up obstacles for foreign GMO developers and so indirectly affect a country's own entrepreneurs. This is at odds with the principle of the free market.[325]

The case studies also revealed that regulatory disconnection in the form of legal uncertainty is not limited to new innovations. The process of adopting new laws and regulations to achieve regulatory reconnection can also lead to legal uncertainty. In both cases, important revisions to EU legislation were hanging over the market and the considerable length of these legislative processes causes long periods of uncertainty about the content of future laws and regulations, which can hinder innovation. The development of cisgenic and other NGT crops and the development of vaccines take a long time and will be more difficult to fund if it is not clear what rules will apply in five- or ten-years' time. Moreover, the cisgenesis case study shows that the lengthy process of adopting the legislative proposal on NGTs is also keeping opponents of the proposal in the dark.[326]

When it eventually becomes clear what the new legislation will look like, new ambiguities may arise concerning the interpretation of new provisions that have not yet been tested in practice, such as the criteria of equivalence for category 1 NGT products in the legislative proposal on NGTs, discussed in § 5.3.3. It will take some time before such substantive ambiguities are addressed by regulatory agencies or in the case law.

The analysis in § 7.2.1 and § 7.2.2 of the regulatory disconnection that came to light in the case studies is summarised in Figure 7.1.

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determining factor in the definition of replication, which is the *ability to replicate rather* than the actual occurrence of replication. De Schrijver, Wijns & Rüdelsheim, 2024, p. 6.

[323] See § 6.2.2.
[324] See § 6.2.3.
[325] Art. 4(2a) TFEU. See also § 7.4.2.
[326] See § 5.3.3.

Figure 7.1 Problem analysis of the green and red biotechnology case studies

Problem	*Nature*
1) Regulatory disconnection as a consequence of GMO status / over-inclusive regulation	1a) Lengthy / expensive administrative requirements that do not apply to non-GMOs with similar risk profiles.
	1b) Political obstruction of marketing authorisation (green biotechnology)
	1c) Cumulation of different procedures (red biotechnology: GMO environmental risk assessment + medical ethical review)
2) Regulatory disconnection caused by legal uncertainty	2a) Differences in interpretation of legal terms between scientists in relation to new technology
	2b) Differences in interpretation of legal terms between EU member states and between member states and the European Commission in relation to new technology
	2c) Uncertainty about the content and interpretation of new EU legislation caused by the slow process of regulatory reconnection via legislative amendment

7.2.3 Needs in practice and robustness

In response to the perceived regulatory disconnection, four needs can be distilled from the case studies: 1) the desire among a significant section of scientists and the industry for easing the administrative burdens and obstacles imposed by the GMO legislation; 2) the desire among other stakeholders for adequate attention to safety and precautionary considerations and/or ethical considerations, which according to some respondents can only be guaranteed by having a separate regime for products of genetic modification; 3) the need for legal clarity; 4) the need for faster and shorter revision procedures when the legislation requires amending.

These four needs resonate with the definition of robust regulation given in § 2.2: robust regulation means regulation that can address technological and scientific developments in a timely and legally robust manner in order to protect public interests and promote (or at least not unnecessarily hamper) innovation. The tension between needs 1 and 2 corresponds with the tension that can arise between two components of the definition of robust regulation, as mentioned above: the tension between protecting public interests, such as safety and consumer choice, and the promotion of innovation.[327] In addition, there can be tension between adaptivity (which is assumed in 'address in a timely manner' in the definition) and legal robustness,[328] which corresponds with the tension that can arise between needs 3 and 4. Rapid revision of the legislation may be necessary to ensure timely legal clarity amid changing circumstances, but rapidly changing legislation can also create ambiguity, for example for investors who need rules that remain stable for a certain period of time.

[327] It should be noted that the protection of public interests component also involves internal tensions, because there are different interests and different perceptions of public interests within society. For example, protecting the freedom to use products that are free of GMOs can lead to curtailing the freedom of others to develop and use GMO products.
[328] See § 2.2.

Figure 7.2 links the summarised problem analysis in Figure 7.1 with the needs identified in the case studies and how they relate to the definition of robust regulation.

Figure 7.2 Problem analysis plus needs for robust regulation in practice

Problem	***Nature***	***Needs in practice***	***Definition of robust regulation § 2.2***
1) Regulatory disconnection as a consequence of GMO status / over-inclusive regulation	1a) Lengthy / expensive administrative requirements that do not apply to non-GMOs with similar risk profiles.	1) Need for easing administrative burdens and obstacles resulting from the GMO regime	Regulation that can address technological and scientific developments in a timely (*need 4*) and legally robust manner (*need 3*) in order to protect public interests (*need 2*) and promote (or at least not unnecessarily hamper) innovation (*need 1*).
	1b) Political obstruction of marketing authorisation (green biotechnology)	2) Need for attention to safety, precautionary and/or ethical considerations (via separate GMO regime)	
	1c) Cumulation of different procedures (red biotechnology: GMO environmental risk assessment + medical ethical review)		
2) Regulatory disconnection caused by legal uncertainty	2a) Differences in interpretation of legal terms between scientists in relation to new technology	3) Need for legal clarity 4) Need for a faster and shorter legislative amendment process	
	2b) Differences in interpretation of legal terms between EU member states and between member states and the European Commission in relation to new technology		
	2c) Uncertainty about the content and interpretation of new EU legislation caused by the slow process of regulatory reconnection via legislative amendment		

In Chapter 3, four categories of building blocks for robust regulation were discussed: abstract formulation of legislation (§ 3.2); temporary and experimental legislation (§ 3.3); judicial law-making (§ 3.4) and regulation by regulatory agencies (§ 3.5). In the following sections we combine these building blocks with insights from the case studies in Chapters 5 and 6 to discuss potentially fruitful ways to promote robustness in biotechnology regulation in the Netherlands and the EU and to address the needs of stakeholders.

7.3 More abstract formulation of legislation

7.3.1 Robustness through a product-based approach?

The ideas that emerged from the case studies for meeting the first and fourth need, easing the administrative burden and obstacles resulting from the GMO regime and faster amendment of the legislation, included solutions that make use of the building blocks from the category of more abstract formulation of legislation discussed in § 3.2. As mentioned in § 7.2.1, some of the

respondents played down the GMO status of crops and vaccines, because whether or not a crop or vaccine is a GMO according to the law does not determine the degree of risk it poses. Various respondents saw more potential in a regulation regime based more on open standards, objectives and values, rather than focusing on specific technologies. This desire to reduce the technology component was usually expressed as a preference for a product-based approach.

Proponents of a product-based approach adhere to the principle that the characteristics of products should be assessed independently of the whether genetic modification was involved in their production. This would put an end to a distinction in the legislation that they feel is irrelevant from a safety point of view. In practical terms, a product-based approach could reduce administrative burdens and obstacles, because the requirements and restrictions applying specifically to GMOs under the current rules would no longer apply. Moreover, proponents of the use of NGTs think that in a product-based approach NGT crops could be more attractive than conventional products because they are at least as safe and are less dependent on the use of pesticides. In addition, a product-based approach could make the regulatory framework more flexible and future-proof, because it would be easier to accommodate new techniques within a regime that does not discriminate against products simply because of the techniques used to make them.

However, there are several reasons why it is unlikely that a product-based approach could help to make the regulatory framework more robust. First, always treating new products on the basis of their characteristics instead of how they were made does not *necessarily* mean that GM crops would not have to undergo an environmental risk assessment, but that GM crops and conventional products would be subject to the same sort of assessment. This could mean additional administrative obligations for non-GM crops, which is at odds with the desire among practitioners to ease the administrative burden.[329]

Second, a pure product-based approach goes against the desire among some stakeholder to retain a separate regime for genetically modified products.[330] Moreover, there appears to be insufficient political and public support for transforming the EU legislation into a product-based approach. It would also be a difficult task both legally and in policy terms, because discrimination of GMOs has been the basis of a whole system of rules built up over decades. Altering this principle would be more of a revolution than a legislative reform, and revolutions are rare in a policy regime characterised by path-dependency and incremental change.[331]

7.3.2 Abstract statutory provisions in combination with delegation

This does not alter the fact that quite apart from a product-based approach, more abstract formulation of legislation can still offer possibilities for robust regulation. A regulatory regime in which products of genetic modification are treated separately could also be made more flexible by making relevant aspects of the legislation less detailed. After all, the more detailed it is, the quicker it will be overtaken by new developments and new knowledge.

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[329] See § 5.3.1 and § 6.3.1.
[330] The second need is mentioned in § 7.2.3.
[331] For path-dependency, see e.g. Kay, 2005. For incremental change, see e.g. the classic article by Lindblom, 1959.

Nevertheless, more abstract formulation of legislation is inconsistent with the third need stated in § 7.2.3, the need for legal clarity. This in turn undermines legal robustness, which we identified as a component of robust regulation. That is why a profitable use of more abstract legislation requires a combination of delegation to a regulatory agency that interprets open standards by defining criteria to turn values or objectives into a yardstick for assessing concrete cases. At lower levels of regulation, the rules can be more detailed and can be amended more quickly. The challenge is to formulate abstract legislation in such a way that it provides sufficient guidance and clarity for regulatory agencies. In Chapters 2 and 3 we discussed the interactive approach to law, highlighting its communicative function. This view presupposes a continuous process of developing standards, which is guided and structured to an important extent by the use of open and aspirational standards. The standards are not set in stone, but are interpreted and specified through their implementation in practice. They convey a certain aspiration or value, which guides this interaction.[332]

The existing regulatory framework has for some time made use of the possibility of delegating detailed provisions to lower legislation, an example being the relation between Directive 2001/18/EC and the Dutch Environmental Management Act, Genetically Modified Organisms Decree and Ministerial Regulation on Genetically Modified Organisms. In the case study on samRNA vaccines, it also emerged that the precise form in which decentralised rules and procedures take shape can make a big difference for the administrative burden and length of the procedures.[333] To make regulations more robust, more use could be made of the possibility of formulating provisions in more abstract terms at the highest legislative level and delegating broader powers to regulatory authorities. The disadvantage of this strategy is that the legislation would be more difficult to comprehend. Delegation implies that stakeholders, including applicants, have to refer to different regulations to find the relevant rule or qualification.

The legislative proposal on NGTs provides an example of how delegation can help to make the legislation and regulations more adaptive. The definitions of category 1 NGT crops and category 2 NGT crops in the main text of the legislative proposal are relatively open: a category 1 NGT crop is a crop that fulfils the criteria of equivalence to conventional plants, set out in Annex I, and a category 2 NGT crop is an NGT plant other than a category 1 NGT plant.[334] Further details of this definition can be found in the annexes, and as discussed in § 5.3.4, the proposal gives the European Commission the power to adapt the criteria of equivalence for category 1 NGT crops in Annex I to scientific and technological progress. At the same time, the definitions of category 1 NGT and category 2 NGT crops are bound by the underlying definition of an NGT crop, which says that it must be a crop obtained by a form of cisgenesis or site-directed mutagenesis, on the condition that it does not contain any foreign genetic material.[335] The flexibility available to the Commission to adapt the criteria of equivalence for category 1 NGT is therefore not unlimited. In § 7.4 we take a more detailed look at the role given to the European Commission in the legislative proposal on NGTs and discuss more generally what regulation by regulatory agencies can contribute to robust regulation.

[332] See § 2.3 and § 3.2.1.
[333] See § 6.3.1.
[334] Art. 3 under 7 and 8 COM(2023) 411 final.
[335] Art. 3 under 2 COM(2023) 411 final.

7.3.3 Derogation as a way out

Besides delegation, the relationship between the highest legislative level and lower levels of regulation can also, and sometimes at the same time, take the form of derogation (also known as deregulation). Whereas delegation involves passing on certain details of the legislation to be interpreted in lower-level regulations and by regulatory agencies, derogation makes an exception to a rule and involves applying adapted and generally more flexible rules to certain situations. The experimental form of derogation, which is by definition temporary, was discussed in § 3.3.1, but derogation can also be used in a more permanent form and without an experimental objective.[336]

The option of abstract statutory standards in combination with more specific regulation at lower levels by regulatory agencies is not always available in the GMO legislation, because many detailed rules and procedures are already laid down and amending them is sometimes not politically feasible. Relevant in this context is the observation by Greer and Trump that in a political system like the EU, with much internal debate and many actors determining the direction of policy, there is a tendency to formulate legislation so there are no open ends.[337] In certain situations, derogation can provide a remedy.

An example of derogation at the national level that came up in the case study on samRNA vaccines[338] is the possibility of applying for authorisation with standard conditions (VOV) under Article 3.24 et seq. Genetically Modified Organisms Decree 2013. If a category of GMOs meets certain conditions, for which it must be demonstrated that these GMOs pose negligible risks to human health and the environment, an administrative relaxation of the normal authorisation procedure for deliberate release for purposes other than placing on the market may be granted. For example, for medical applications that meet certain conditions, Article 3.26a of the Genetically Modified Organisms Decree 2013 provides for a much faster authorisation procedure than normal in which certain EU and national public consultation procedures are left out.[339]

Derogation can also take place at the EU level. In fact, the whole legislative proposal on NGTs is one big example of derogation in which two broad categories of GMOs are more (category 1 NGT plants) or less (category 2 NGT plants) exempted from the requirements of the existing GMO legislation. The politically problematic route of revising Directive 2001/18/EC and related legislation was avoided, and the definition of a GMO left intact. But the term GMO may become a lot less relevant through the introduction of the term NGT and the different provisions associated with it. The existing legislation remains in force, but is largely bypassed by the addition of new legislation, which is also more adaptive with a view to future developments. For legislation that is difficult to revise and provides too little leeway for adaptive regulation at lower levels, derogation in a limited or extensive form can provide a way out.

[336] Cf. Du & Heldeweg, 2018, p. 294.
[337] Greer & Trump, 2019; for a more extensive discussion of this, see § 3.5.1.
[338] See § 6.3.1.
[339] Based partly on further information on the background of the VOV from an employee of the Ministry of Infrastructure and Water Management, obtained via Marie-Louise Bilgin, member of the supervisory committee.

It should be noted, though, that derogation to bypass existing legislation because it is difficult to revise for political reasons is hardly elegant. It would be legally more graceful to tackle the core problem in existing legislation, also because that would improve the accessibility of the regulatory framework. The way in which the legislative proposal on NGTs makes use of derogation simply adds a new legal phenomenon to Directive 2001/18/EC, without it being sufficiently clear from the various regulations that the practical relevance of Directive 2001/18/EC is most likely to diminish significantly as soon as the NGT proposal becomes law. In that sense, it can be considered to be a suboptimal solution.

7.4 Regulation by regulatory agencies

7.4.1 Reduced tension between adaptivity and legal certainty

As became clear in § 7.3, delegation of regulatory powers to regulatory agencies can be seen as an important building block for robust regulation, preferably in combination with overarching legislation containing provisions formulated in abstract terms that offer sufficient scope for adaptivity at lower levels of regulation. In the case studies, various examples were put forward which clearly showed that regulatory agencies are better able to provide legal certainty *and* adaptivity than the legislature, even when the overarching legislation provides little scope for it. This would suggest that the tension between legal robustness and adaptivity, crucial elements in the definition of robust regulation and corresponding with needs 3 and 4,[340] can best be reduced at lower levels of regulation. Best practices for this are the use of standard permit conditions (VOV) discussed above[341] and the frequency with which lists of safe techniques for contained use in annexes to the Ministerial Regulation on Genetically Modified Organisms (GMO Regulation) can be amended: every three months, which is fairly often.

However, interests may conflict. Researchers and applicants tend to want more, and soon,[342] whereas regulatory agencies have a different task. They have to find a balance between commercially feasible innovations and the interests of human health and the environment. The aim is, or should be, to harmonise these interests by stimulating innovations that benefit humans and the environment.[343] Policy officers at the Ministry of Infrastructure and Water Management's GMO Office are willing to make the authorisation procedures simpler and more efficient, but their goodwill is restricted by their need to comply with national and EU legal frameworks and deadlines.

7.4.2 Centralisation or decentralised delegation

When it comes to delegating regulatory powers under EU legislation, the question is what is best for robust regulation: delegation to regulatory agencies in the member states or to regulatory agencies at the EU level? The existing examples in the case studies mainly concern delegation to national regulatory agencies. The advantage of this is that they know the national situation best and are best able to align their regulatory activities with it. The disadvantage is that this can lead to differences in GMO legislation between member states, which does not help legal

[340] See § 7.2.3.
[341] See § 6.3.1 and § 7.3.3.
[342] Cf. needs 1 and 4, § 7.2.3.
[343] Cf. needs 2, § 7.2.3.

clarity. Moreover, differences between member states can lead to unfair competition and create tension with the principle of the free single market in the EU.[344]

In both case studies, however, a tendency towards centralisation at the EU level can be seen, particularly in the legislative proposals for NGTs and for medicinal products. As discussed above, the legislative proposal on NGTs gives the European Commission an important role. If the relevant provisions remain in force in the adopted regulation, the Commission will have the power to adapt the criteria of equivalence for category 1 NGT plants in line with the changing scientific and technological landscape. This will considerably increase the adaptivity of the legislation, while placing this power at the centre with the European Commission will prevent differences in national interpretations from arising. When defining what does and does not belong in category 1 NGT, as with determining what does and does not fall within the definition of a GMO, differences between member states is not desirable given the legal contradictions in the definition that this would entail.

The centralisation in the proposed legislation for medicinal products makes the EMA responsible for the environmental risk assessment and the medical ethical review of clinical trials of medicines or therapies made using GMOs. The authorisation procedure for placing GMO medicines on the market already lies at the EU level, but the responsibility for the environmental risk assessment of clinical trials currently lies at the national level. Consolidating and centralising the two procedures in a single European regulatory agency would have several advantages. Consolidating these procedures may help to reduce the administrative burden, although some respondents fear that the specific national arrangements they are now comfortable with will be scrapped, resulting in an even greater administrative burden (need 1). Centralisation could eliminate potential inconsistencies between national interpretations of the GMO legislation.[345] It could also help to remove the ambiguity surrounding the environmental risk assessment (need 3). The inevitable downside of such a centralisation of these responsibilities is that member states and their agencies would have less control over the process, which could be particularly problematic if national authorities feel that European agencies interpret the legislation incorrectly or in an undesirable way.[346]

It is difficult to draw general lessons on the choice between decentralisation and centralisation. Both can have advantages and disadvantages. It will probably depend on the specific situation whether delegation to the centre or to lower levels is the best option. It would seem that defining and amending criteria for core categories such as category 1 NGT is best delegated to the central EU level, because the interest of having of clear and consistent definitions at the EU level outweighs the interest of scope for national discretion. At the same time, it can be questioned how much use the European Commission will make of this power. The Commission may be slower to respond than national bodies, partly because it has to deal with many more stakeholders.[347]

[344] See § 7.2.2.
[345] See § 6.2.3 and § 7.2.2.
[346] Cf. § 7.2.2.
[347] See § 6.3.1.

7.4.3 Legitimacy of delegated regulation

Regulatory agencies can generally act more quickly than the legislature, because they are subject to fewer checks and balances. For this reason, questions can be raised about the constitutional and democratic legitimacy of regulation by regulatory agencies. The legislative proposal on NGTs shows that it is possible to find a reasonable balance between adaptivity and legitimacy. Although the proposal is not yet definite and it is as yet unclear how it will work in practice, delegating the power to amend the criteria of equivalence for category 1 NGT plants to the European Commission would seem to have several strong points, at least on paper.

First, the Commission is the head of the executive branch of the EU and therefore occupies the strongest possible position of all regulatory agencies to which this task could have been delegated. Second, the form in which this delegation has been structured ensures that the Commission could not operate without political support from the member states and the European Parliament, while at the same time leaving little room for delaying or obstructive politics. This seems to provide at least a minimum assurance that the Commission will exercise this power in a legitimate manner.[348] Third, the Commission is political enough to take political interests into account and technocratic enough not to allow political considerations to overshadow technological and scientific considerations.

However, there are some concerns. It can be questioned how broad the scope of the European Commission's deliberations will be when amending the criteria of equivalence for category 1 NGT plants. The relevant provision only states that the Commission will consult experts designated by each member state, which entails the risk that certain types of relevant expertise, such as bottom-up social knowledge and ethical knowledge, will be largely left out of consideration. For really robust regulation it is important that the regulation-to-society connection and the regulation-to-ethics connection are guaranteed.[349] Various respondents mentioned the importance of public support for a good reason.

It can also be questioned whether members of national parliaments and the European Parliament will be prepared to transfer such powers to the European Commission or other regulatory agency. And as regulatory agencies have close contacts with the industry, would they be more susceptible than the legislature to 'regulatory capture', in which industry interests would be allowed to outweigh public interests?

7.5 Temporary and experimental regulation

7.5.1 Experimental regulation: legal innovation or tradition?

Various aspects of the case studies fall within the concept of temporary and experimental legislation, such as the importance of regular evaluations and reviews stressed by some respondents.[350] The power delegated to the European Commission to amend the category 1 NGT criteria of equivalence is also temporary, but in the absence of a political majority in the European Parliament and Council to revoke this power it will be automatically extended.[351]

[348] See § 5.3.4.
[349] See § 2.3.
[350] See § 5.3.5 and § 6.3.4.
[351] See § 5.3.4.

The proposed new legislation on medicinal products contains provisions that should make regulatory sandboxes possible. According to the theory discussed in § 3.5.2, regulatory sandboxes are actually an instrument of regulatory agencies, which can even deploy them in spite of the regulations, but this theory has been debunked by the EU legislature, which prefers to have control over regulatory sandboxes and has therefore incorporated them into the legislation. This considerably whittles down the difference between regulatory sandboxes and experimental legislation in this case.

The aim of regulatory sandboxes in the legislative proposal for medicinal products is to address any problems in the regulatory regime and to facilitate future innovation.[352] More specifically, the regulatory sandboxes are intended to test the development, clinical trials and placing on the market of certain medicinal products under certain conditions. These experiments are facilitated independently of the authorisation procedure under the responsibility of the EMA and the competent national authorities. Among the respondents in our study there was some reticence about such test environments,[353] including the question of the irreversibility of measures. Another concern was who would be responsible if things go wrong.[354] This last concern seems to be addressed in Articles 113 and 114 of the proposal for a Regulation. The EMA has the final responsibility and the European Commission also has to give its approval for a regulatory sandbox. However, it is conceivable that these bodies will seek to pass on responsibility for any risks as far as possible by requiring the experimenting party to take various mitigating measures. This would make the attractiveness of sandboxing a cost-benefit exercise.[355]

Respondents also pointed to the reservations concerning experimental legislation and regulatory sandboxes discussed in Chapter 3. There is a tendency to evaluate the intended effects of experiments from the top down and ignore bottom-up social knowledge. The legal fragility of experiments is another concern. Experiments are legally fragile from the perspective of legal equality, because companies participating in an experiment come under a more favourable regulatory regime than companies within the same jurisdiction that are not participating in an experiment. In addition, experiments can affect legal certainty because temporary and/or local deviations make it more difficult to ascertain the applicable rules, and because there may be tension between the temporary nature of experimental rules and the expectations they raise for the future after the experiment has come to an end.[356] According to the literature, the reservations concerning legal equality and legal certainty also apply to regulatory sandboxes, and even more forcefully as they have no firm legal basis.[357] This last point does not seem to apply to sandboxes in the legislative proposal for medicinal products because under the proposal they would be given a legal basis.

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[352] *BNC-fiche Herziening EU farmaceutische wetgeving.* Art 113, Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006.
[353] Interview with senior project leader, molecular virology, BSO and associate director global regulatory affairs, MSD Animal Health; interview with senior advisor on gene technology and biological safety, RIVM.
[354] Cf. § 3.5.3 on the reservations concerning sandboxes in the literature.
[355] With thanks to Prof. Evert Stamhuis for his addition.
[356] See § 3.3.2.
[357] See § 3.5.3.

The above does not mean that experimental regulation is by definition problematic. It could even be said that experimental regulation has a long tradition in the regulation of GMOs. For example, the regulation of field trials with GM crops can be seen as a form of experimental regulation, because GMOs that have not yet been approved for cultivation or placing on the market may be cultivated temporarily on a defined plot under certain conditions. Such trials allow a better understanding of the characteristics of the crop to be obtained to inform a decision on authorisation on a larger scale and on a permanent basis. Over the years, such field trials have withstood public resistance and legal challenges and can now be seen as an accepted instrument which causes relatively little unrest.[358]

7.5.2 Temporary regulation as a lever for adaptivity

However, the largest part of the GMO legislation does not meet the requirement for temporary legislation or provisions with or without an experimental goal described in § 3.3, which is that in contrast to normal laws they expire unless action is taken to extend them. This requirement means that the introduction of temporary provisions in future amendments of the GMO legislation, such as the legislative proposal on NGTs, could have an added value. Temporary legislation has several advantages. It increases the willingness to reach a consensus on temporary legal frameworks and standards, as member states are not committed to these frameworks for an undetermined period.[359] Experiences with the GMO legislation show that it is difficult to break deadlocks and adapt the legislation to new developments.[360] Within and between member states there are many political controversies which block the path to any agreement and the current regulatory frameworks remain in force. If proposed legislation is temporary, member states may be more inclined to consent. Another advantage is that temporary legislation forces legislative bodies to evaluate the regulations, revise them or extend them when they expire. These evaluations and revisions can also take technological developments into account, thus addressing the pacing problem.[361]

A possible disadvantage, certainly in the current GMO debate, is that the political controversies that make amending the legislation more difficult can also stand in the way of extending or revising temporary legislation. There is a risk that some legislation or specific provisions will then expire, which would be welcome for some stakeholders, but certainly unwelcome for others. This disadvantage could be obviated by temporary legislation in the form of regulations based on a framework directive. Should the temporary regulation nevertheless not be extended due to political controversies or other reasons, the directive would still be in force. However, in such a situation the legal uncertainty will be greater than before the regulation was in force.

It should be noted, however, that there is a tendency among legislators actors in the EU, mentioned several times already, to make detailed legislation that bind each other and their successors to the provisions.[362] It is questionable whether they will overcome this inclination and draw up more adaptive rules. This may frustrate the feasibility of this solution strategy,

[358] Cf. § 5.2.1.
[359] See § 3.3.1.
[360] Mampuys & Poort, 2019.
[361] As well as need 4, as identified in § 7.2.3.
[362] Greer & Trump, p. 511–512.

unless temporary regulations are combined with delegation and temporary provisions are applied at lower regulatory levels.

7.6 Judicial law-making

In § 3.4 we discussed the contribution that judicial law-making could make to the robustness of technology regulation. The courts have a good track record when it comes to flexibility and the ability to adapt rules to new developments. They can take decisions more quickly than legislators can make new rules and they can meet the need for legal clarity, legal certainty and legal equality.[363] This means that judges have a role to play both in the adaptivity and the legal robustness of GMO legislation.

Nevertheless, too much must not be expected of judicial law-making in this specific context. This was illustrated by the decision in 2018 by the CJEU (see also Box 2.1) in which European judges addressed the question of whether techniques of site-directed mutagenesis, or gene editing, should fall under the exception granted to mutagenesis.[364] There were high expectations of this decision and many stakeholders hoped that the Court would do what the legislature had neglected to do: break the legal impasse. The CJEU did not take this opportunity and ruled that site-directed mutagenesis does not fall under the exception. No room was created for flexibility to facilitate or stimulate innovation.[365]

It is therefore a somewhat unpredictable and risky strategy to leave it to the courts to create more flexibility in the legal framework. The fact that courts can interpret rules in the light of new developments does not mean that they will do so. Moreover, there are further disadvantages, discussed in § 3.4.3, related primarily to the fact that an adaptive interpretation of EU legislation that also provides legal certainty can only really be expected from the CJEU. This is a time-consuming route with considerable obstacles along the way, which moreover can only be pursued when there is a case and the parties involved decide to take it to court for a decision (in the highest instance).

7.7 Conclusion: building blocks for robust regulation

In this report we have presented an analysis of grey areas and, based on a literature study and case studies, we have identified and described the possibilities for addressing this problem by making regulation more robust. The theoretical discussion in Chapter 3, the empirical investigation in Chapters 5 and 6 and the insights derived from these chapters in § 7.3 to § 7.6 have provided a balanced picture of building blocks for robust regulation. It can be concluded that there is no single clear-cut, easy-to-use option for make biotechnology regulation more robust. Rather, it is a question of a variety of modest measures, each addressing different needs identified in § 7.2.3, but also each with its own pitfalls.

That each building block has its advantages and disadvantages does not mean that it makes no difference which building block is used. Not all advantages and disadvantages carry equal

[363] It should be noted, however, that the court's ruling will only be given if one of the interested parties submits a request to the court. This is often preceded by a lengthy and slow process.
[364] CJEU 25 July 2018, C-528/16, ECLI:EU:C:2018:583 *(Confederation paysanne et al. tegen Premier ministre en Ministre de l'agriculture, de l'agroalimentaire et de la forêt)*.
[365] Bergmans et al., 2020.

weight, nor do they have the same weight in every context. It is therefore important to weigh up the potential contribution of different building blocks and their drawbacks in each context, and on that basis determine the combination, precise form and dose in which these building blocks can best be used. As a guide, Figure 7.3 at the end of this chapter provides a summary overview of the advantages and disadvantages of the various building blocks identified from our theoretical and empirical research. Where possible, we have stated which needs these advantages and disadvantages affect or how they relate to the definition of robust regulation.

Although the specific use of the building blocks must be determined on a case-by-case basis, striking a balance between advantages and disadvantages, our research suggests state that in general the following building blocks have the greatest potential for creating a more robust regulation of rapidly changing biotechnology, preferably when used in combination:

1) the use of more abstractly formulated rules in legislation that are less likely to be overtaken by new developments (or, if necessary, bypassing detailed and static rules through derogation);
2) regulation by regulatory agencies with an adequate mandate to quickly adapt regulations to new developments;
3) temporary or experimental provisions in legislation or lower-level, which can serve as a lever to ensure regulations are actually adapted to new developments.

Some of these building blocks are already being used, especially the second one, but there is room to make much greater use of all three, possibly in new ways as well. The theoretical analysis, the case studies and this concluding chapter provide inspiration and draw attention to a number of conditions and issues to be addressed.

The above list of most suitable building blocks does not include judicial law-making. This is not to deny that the courts have a role to play in the robust regulation of biotechnological developments, but the independent role of the courts in combination with a case-oriented approach, the consequences of which are discussed in § 3.4 and § 7.6, means that judicial law-making is not well suited to a governmental exercise to make regulation more robust.

Finally, in § 2.3.3 we ascertained that it is only meaningful to consider robust regulation once its fundamentally political nature is recognised. At both the EU and national levels, political actors are almost always involved in the development and amendment of regulations. The question of whether or not there is sufficient public and political support for stimulating innovation in gene technology is always a consideration. This may be different in each member state and for each topic. Public resistance to the development of GM vaccines is less than to GM crops. However, even for GM vaccines there are changes in society that could affect the political will to facilitate these developments.

This means that public support and political will always play a role in the background to the solution strategies we put forward. This is illustrated in Figure 7.3. If a solution strategy requires a revision of EU legislation, this can raise additional hurdles to be overcome. At the national level, at least in the Netherlands, these hurdles may be smaller, but should not be underestimated.

Figure 7.3 Needs and building blocks for robust regulation

Needs in practice			
1) Need for easing administrative burdens and obstacles resulting from the GMO regime	2) Need for attention to safety, precautionary and/or ethical considerations (via a separate GMO regime)	3) Need for legal clarity	4) Need for a faster and shorter legislative amendment process
Definition of robust regulation			
Regulation that can address technological and scientific developments in a timely (*need 4*) and legally robust manner (*need 3*) in order to protect public interests (*need 2*) and promote (or at least not unnecessarily hamper) innovation (*need 1*).			
Building blocks for robust regulation			
1 More abstract formulation of legislation	*Advantages*	*Disadvantages*	
Product-based approach	-No specific requirements for GMOs (need 1) -Easier to accommodate new technology (need 4)	-A product-based approach is difficult to reconcile with need 2 -Possible additional administrative requirements for non-GMOs (need 1) -Unfeasible for political, social, legal and policy reasons	
Abstractly formulated provisions in legislation combined with delegation of powers to regulatory agencies	-Less detail makes legislation less likely to be overtaken by events, lower-level regulations are more adaptive (need 4) -Use of a tried and tested method increases feasibility	-Abstractly formulated provisions can provide less certainty and guidance, delegation to lower levels makes regulations harder to comprehend (need 3) -Less control by the institutions of representative democracy; see also below under 2) Regulation by regulatory agencies	
Derogation	-Makes it possible in certain situations to bypass difficult to revise legislation	-Use of exceptions and derogation is a suboptimal alternative to updating legislation, partly because they make regulation harder to comprehend (need 3)	
2) Regulatory agencies	*Advantages*	*Disadvantages*	
Regulation by regulatory agencies	-Depoliticisation ensures greater adaptivity of regulations (need 4) -Regulatory agencies are more able than the legislature to reconcile adaptivity and legal certainty (needs 4 and 3)	-Depoliticisation can make the democratic trade-off between protecting public interests and promoting innovation more difficult (definition of robust regulation), with the risk that social and ethical aspects may be insufficiently taken into account (need 2) -Risk of regulatory capture (need 2) -Regulation by regulatory agencies depends on latitude in the legislation	
Delegation to regulatory agencies at the member state level	-National bodies are best able to tailor regulation to the situation in their member state -National bodies may be able to adapt regulation more quickly than EU agencies (need 4)	-Can lead to differences in regulation and interpretation between member states and between member states and EU agencies at the expense of legal clarity (need 3)	

	-Better addresses the desire for control by member states and their agencies	-Can create tension with the EU principle of the single market.
Delegation to regulatory agencies at the EU level	-Promotes legal clarity by avoiding differences between regulations and centralising interpretation (need 3) -Enables a reduction in the administrative burden by integrating cumulative procedures (need 1) -Pool of experts is bigger, increasing the likelihood of sufficient expertise	-EU agencies may be slower to adapt regulations than national agencies (need 4) -Possible increase in administrative burdens because existing specific national regulations must be scrapped (need 1) -Less control by member states and their agencies -Doubts about the political feasibility because member states and their parliaments must be prepared to give up control
3 Temporary and experimental regulation	*Advantages*	*Disadvantages*
Temporary legislation	-Can improve adaptivity because it may be easier to reach consensus on temporary provisions -Can improve adaptivity because temporary provisions require regular evaluation, revision or extension (need 4)	-A failure to reach agreement on future temporary provisions creates legal uncertainty (need 3) -Doubts about political feasibility as the tendency of legislators to bind each other and their successors to the provisions in the future has to be relinquished
Experimental regulation / regulatory sandboxes	-Makes it possible to get to grips with the 'unknowns' of new technological applications and (alternative) regulation of these applications by gaining practical know-how on a limited scale, addressing the pacing problem and the Collingridge dilemma (need 4), which can be beneficial for both the need to protect public interests (need 2) and the need to promote innovation (need 1); (see also the definition of robust regulation)	-A more favourable regime for experimenting businesses creates legal inequality (legal robustness and the definition of robust regulation) -Exceptions and derogations can lead to a reduction in the precautionary/protection function of regulations to the disadvantage of public interests (need 2) -Exceptions and derogations make regulations harder to comprehend (need 3) -Experimentation can affect legal certainty because it raises expectations inconsistent with the temporary nature of the experiment (legal robustness definition of robust regulation) -A clear division of responsibilities between regulatory agencies and the experimenting business is difficult to achieve and/or the necessary safeguards may be administratively burdensome (need 1)
4 Judicial law-making	*Advantages*	*Disadvantages*
	-The courts can provide more adaptivity than the legislature -The courts can address the need for legal clarity (need 3), legal certainty	-Legally robust adaptivity is a time-consuming route with significant hurdles to the highest courts, especially the Court of Justice of the EU, which depends on

	and legal equality (legal robustness definition of robust regulation)	having a suitable case with committed parties (need 4) -In court rulings, adaptivity and legal robustness are not always in balance (definition of robust regulation) -The position of the courts is less suited to balancing conflicting social desires, values and interests. -Effecting change through judicial law-making is generally a gradual process (need 4)

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Legislation

European Union legislation

- Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms.
- Directive 2009/41/EC of the European Parliament and of the Council on the contained use of genetically modified micro-organisms.
- Directive (EU) 2015/412 of the European Parliament and of the Council amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory.
- Treaty on the Functioning of the European Union.
- Regulation (EC) No 178/2002 of the European Parliament and of the Council laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.
- Regulation (EC) No 1829/2003 of the European Parliament and of the Council on genetically modified food and feed.
- Regulation (EC) No 1830/2003 of the European Parliament and of the Council concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC.
- Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.
- Regulation (EU) No 535/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use.
- Regulation (EU) 2020/1043 of the European Parliament and of the Council on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19).
- Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC (COM (2023) 192 final).
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- Proposal for a Regulation of the European Parliament and of the Council on plants obtained by certain new genomic techniques and their food and feed, and amending Regulation (EU) 2017/625 (COM(2023) 411 final).
- European Parliament legislative resolution of 24 April 2024 on the proposal for a Regulation of the European Parliament and of the Council on plants obtained by certain new genomic techniques and their food and feed, and amending Regulation (EU) 2017/625 (COM(2023)0411 – C9-0238/2023 – 2023/0226(COD)).

National legislation

- *Wet Medisch-wetenschappelijk Onderzoek met mensen*.
- *Besluit van 3 mei 2024 tot vaststelling van het tijdstip van inwerkingtreding van artikel III van het Besluit van 20 oktober 2022 tot wijziging van het Besluit genetisch gemodificeerde organismen milieubeheer 2013 (uitvoering verordeningen (EU) 2019/1381 en (EU) 2020/1043) (Stb. 2022, 407)*.
- *Besluit genetisch gemodificeerde organismen milieubeheer (2013)*.
- *Regeling genetisch gemodificeerde organismen milieubeheer (2014)*.
- *Gezondheids- en welzijnswet voor dieren*.

Parliamentary papers and official government documents

- *Aanhangsel Handelingen II* 2012/13, nr. 207.
- *Kamerstukken* II 2011/12, 27 428, nr. 230.
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- EMA/392588/2024 Kostaive | European Medicines Agency (EMA).

Court rulings

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- Opinion of Advocate General Bobek 18 January 2018, C-528/16, ECLI:EU:C:2018:20.
- Hoge Raad 20 december 2019, ECLI:NL:HR:2019:2006 (Urgenda).
- Gerechtshof Den Haag 12 november 2024, ECLI:NL:GHDHA:2024:2099 (Shell).

Appendix 1 Interview topics for the cisgenesis in agriculture case: DuRPh project

Introduction
The aim of this study was to learn more about how biotechnological developments are linked to the emergence of ambiguities in the application of the existing regulatory framework (grey areas) and how these ambiguities can be addressed by a different (more robust) wording of the legislation. In two case studies we tried to obtain a better understanding of the causes and problems of grey areas and of the needs among practitioners to provide long-term solutions for dealing with these grey areas.

Case
The DuRPh project aimed to use cisgenesis to develop a potato variety resistant to the potato disease *Phytophthora*. The use of cisgenesis to make potato varieties resistant to this disease can be considered to be a grey area. The statutory definition of a genetically modified organism is stated in Article 2 of Directive 2001/18/EC:

> 'genetically modified organism (GMO)' means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.'

It therefore means an organism whose genetic material is not present in nature or cannot be obtained by conventional breeding methods. The potato varieties developed in the DuRPh project do not contain any foreign genes. In addition, the potato varieties can also be incrossed using conventional methods, but that process is complicated and complex. Cisgenesis speeds up this process and the result is the same.

The question, therefore, is whether this application does or does not fall within the definition of a GMO. Relevant to this is the 2015 decision by the Court of Justice of the EU that cisgenesis is a gene technology and that the use of cisgenesis does fall within the scope of Directive 2001/18/EC.[366] Labelling this case a grey area raises the question of the lower limit, the need for an exception to the legislation and the question of the purpose and value of the risk assessment in comparison with conventional breeding methods.

General
- Personal role/involvement in DuRPh, use of cisgenesis in agriculture?
- Opportunities and risks of cisgenesis in agriculture?

Grey areas
- Regulation of cisgenesis in agriculture?
- Do you think the existing rules are suitable for addressing the opportunities and/or risks of cisgenesis? Why/Why not?
- Ambiguities in the legislative framework?
- Problems in the application of the legislative framework?

[366] Case C-528/16, C*onfédération paysanne and Others v Premier Ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Fo*rêt ECLI:EU:C:2018:583.

- Expectations for a new legislative framework?
- Explanation for these ambiguities or limitations?
- Relationship between laws and rules and the opinions and accepted practices ‘in the field’?
- Attitude of decision-makers/licensing authorities?
- Obstacles outside the legal frameworks?

Need for robustness and solution strategies

- What improvements are needed?
- Should existing rules or procedures be changed?
- Flexibility in the new legal framework?
- Relevant sources of knowledge that should be consulted when amending the regulatory framework (ethical, economic, social, biotech, sustainability)?
- Future-proofing?
- Options for flexibility?
- Relationship between Dutch and EU political and societal context?

Appendix 2 Interview topics for the self-amplifying messenger RNA vaccines (samRNA) case

Introduction
The aim of this study was to learn more about how biotechnological developments are linked to the emergence of ambiguities in the application of the existing regulatory framework (grey areas) and how these ambiguities can be addressed by a different (more robust) wording of the legislation. In two case studies we tried to obtain a better understanding of the causes and problems of grey areas and of the needs among practitioners to provide long-term solutions for dealing with these grey areas.

Standard mRNA vaccines do not fall within the scope of the GMO regulations as they are not derived from an organism. At the same time, vaccines based on recombinant viral vectors do fall under the EU legislation on genetically modified organisms (GMOs). This applies to both vector vaccines and self-spreading vaccines. It can therefore be argued that self-amplifying mRNA vaccines (samRNA vaccines) may also fall within the scope of the regulations, even though, like standard mRNA vaccines, they could also fall outside the GMO legislation because they are not derived from an organism.

General
- Personal role/involvement with samRNA vaccines?
- Opportunities and risks of samRNA vaccines?

Grey areas
- Regulation of samRNA vaccines?
- Do you think the existing rules are suitable for addressing the opportunities and/or risks of samRNA vaccines? Why/Why not?
- Ambiguities in the legislative framework?
- Expected problems in the application of the legislative framework?
- Explanation for these ambiguities or limitations?
- Relationship between laws and rules and the opinions and accepted practices 'in the field'?
- Attitude of decision-makers/licensing authorities?
- Obstacles outside the legal frameworks?

Need for robustness and solution strategies
- What improvements are needed?
- Should existing rules or procedures be changed?
- Relevant sources of knowledge that should be consulted when amending the regulatory framework (ethical, economic, social, biotech, sustainability)?
- Future-proofing? Flexibility of the legal framework?
- Options for flexibility?
- Relationship between Dutch and EU political and societal context?

Appendix 3 List of respondents

Cisgenesis in agriculture: DuRPh project

- Plant breeding researcher, Wageningen University & Research (WUR)
- Team leader, applied ecology, WUR
- Member of the Subcommittee on Agriculture (ScL) COGEM and epigenetics researcher, Vrije Universiteit Amsterdam
- Director of Plantum (trade association for the breeding, propagation and cultivation of seeds and young plants)
- Policy officer, Plantum
- Programme director, hollandbio (association of biotechnology companies)
- Project manager sustainable future, hollandbio
- Director of Odin (cooperative supermarket for organic food)
- Senior advisor on gene technology and biological safety, (RIVM)
- Senior policy officer for biotechnology, Ministry of Agriculture, Fisheries, Food Security and Nature (LVVN)
- Senior policy officer for organic agriculture, LVVN
- Policy officer for biotechnology safety, Ministry of Infrastructure and Water Management (IenW) (policy officer A)

samRNA vaccines

- Member of the Subcommittee on Medical and Veterinary Aspects (ScMV) COGEM and Professor of Arbovirology & Medical Biotechnology, Wageningen University & Research (WUR)
- Professor of Tumour Virology, University Medical Center Groningen (UMCG)
- Professor of Applied Molecular Oncology, Amsterdam University Medical Center (Amsterdam UMC) and chair of the Netherlands Society of Gene and Cell Therapy (NVCGT)
- Associate director global regulatory affairs, MSD Animal Health
- Senior project leader, molecular virology, MSD Animal Health
- Biological safety officer, MSD Animal Health
- Biological safety officer / environmental safety officer, Biosafety Support
- Senior advisor on gene technology and biological safety, National Institute for Public Health and the Environment (RIVM)
- Scientific staff member, Central Committee on Research Involving Human Subjects (CCMO)
- Policy officer for biotechnology safety, Ministry of Infrastructure and Water Management (IenW) (policy officer A)
- Policy officer for biotechnology safety, Ministry of Infrastructure and Water Management (IenW) (policy officer B)