Contribution ID: 1d2f2073-ab05-46af-bb5b-7063db2dd0ce
Date: 15/05/2020 17:55:33

Stakeholder questionnaire on new genomic techniques to contribute to a Commission study requested by the Council

Fields marked with * are mandatory.

Questionnaire on new genomic techniques to contribute to the study requested by the Council

Discussed and finalised in the Ad-hoc Stakeholder meeting on 10 February 2020

Background

The Council has requested [1] the Commission to submit, by 30 April 2021, "a study in light of the Court of Justice's judgment in Case C-528/16 regarding the status of novel genomic techniques under Union law" (*i.e.* Directive 2001/18/EC, Regulation (EC) 1829/2003, Regulation (EC) 1830/2003 and Directive 2009/41/EC).

To respond to this Council's request, the Commission is collecting contributions from the stakeholders through the questionnaire below. The study covers all new genomic techniques that have been developed after 2001.

Instructions

For the purpose of the study, the following definition for new genomic techniques (NGTs) is used: techniques that are capable of altering the genetic material of an organism and which have emerged or have been developed since 2001 [2].

Unless specified otherwise, the term "NGT-products" used in the questionnaire covers plants, animals, micro-organisms and derived food and feed products obtained by NGTs for agri-food, medicinal and industrial applications and for research.

Please substantiate your replies with explanations, data and source of information as well as with practical examples, whenever possible. If a reply to a specific question only applies to specific NGTs/organisms, please indicate this in the reply.

Please indicate which information should be treated as confidential in order to protect the commercial

interests of a natural or legal person. Personal data, if any, will be protected pursuant to Regulation (EU) 2018/1725 [3].

[1] Council Decision (EU) 2019/1904, OJ L 293 14.11.2019, p. 103-104, https://eur-lex.europa.eu/eli/dec/2019/1904/oj
[2] Examples of techniques include: 1) Genome editing techniques such as CRISPR, TALEN, Zinc-finger nucleases, mega nucleases techniques, prime editing etc. These techniques can lead to mutagenesis and some of them also to cisgenesis, intragenesis or transgenesis. 2) Mutagenesis techniques such as oligonucleotide directed mutagenesis (ODM). 3) Epigenetic techniques such RdDM. Conversely, techniques already in use prior to 2001, such as Agrobacterium mediated techniques or gene gun, are not considered NGTs.
[3] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC, OJ L 295, 21.11.2018, p. 39–98

Guidelines

Please note that the survey accepts a maximum of 5000 characters (with spaces) per reply field. You might be able to type more than 5000 characters, but then the text will not be accepted when you submit the questionnaire. You will also receive a warning message in red colour below the affected field.

You have the option to upload supporting documentation in the end of each section. You can upload multiple files, up to the size of 1 MB. However, note that any uploaded document cannot substitute your replies, which must still be given in a complete manner within the reply fields allocated for each question.

You can share the link from the invitation email with another colleague if you want to split the filling-out process or contribute from different locations; however, remember that all contributions feed into the same single questionnaire.

You can save the draft questionnaire and edit it before the final submission.

You can find additional information and help here: https://ec.europa.eu/eusurvey/home/helpparticipants

Participants have until 15 May 2020 (close of business) to submit the questionnaire via EUsurvey.

QUESTIONNAIRE

Please provide the full name and acronym of the EU-level association that you are representing, as well as your Transparency Registry number (if you are registered)

If the name of the association is not in English, please provide an English translation in a parenthesis

EuropaBio.
EuropaBio is the European Association for Bioindustries.
Our Transparency registry number is 1298286943-59.

Please mention the sectors of activity/fields of interest of your association

EuropaBio is the recognised voice of the European biotech community championing world-class solutions for society's challenges. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a bio-based and zero-waste economy.

If applicable, please indicate which member associations (national or EU-level), or individual companies /other entities have contributed to this questionnaire

EuropaBio represents 81 corporate and associate members and bio regions, and 15 national biotechnology associations in turn representing over 1800 biotech SMEs at a Member State level: https://www.europabio.org/about-us/members

If applicable, indicate if all the replies refer to a specific technique or a specific organism

The three main sectors of biotechnology in healthcare, industrial process and agriculture have all contributed to our replies, and our replies generally refer to all applications of NGTs relevant for these three sectors.

We indicate in our replies which part of the reply pertains to which (group of) organism(s). In terms of techniques, our replies generally cover all NGTs, although in some replies we clearly refer to genome editing techniques.

In healthcare biotechnology, our replies refer to advanced therapy medicinal products (ATMPs) and more specifically to gene therapies, including gene therapies using genome editing technologies in vitro, for human use.
As per our understanding, in vivo application of gene therapies using genome editing technologies is outside the scope of this study.

A - Implementation and enforcement of the GMO legislation with regard to new genomic techniques (NGTs)

* **1. Are your members developing, using, or planning to use NGTs/NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide details

- The majority of EuropaBio's member companies are developing, using, or planning to use NGT-derived products. However, many applications are likely to be delayed in the EU compared to other continents, due to the EU's partly dysfunctional authorisation system for genetically modified organisms, which currently applies to NGT-derived products, even when these products are not transgenic.

- Healthcare Biotechnology:

In medicine, gene therapies or other types of advanced therapies may be delivered though a carrier - a vector which is genetically engineered though the use of NGTs and other gene technologies to deliver a normal copy of a malfunctioning or missing gene. Certain viruses are often used as vectors and NGTs are used to modify them so they cannot cause disease when used in people. Some types of viruses, such as retroviruses, integrate their genetic material (including the gene they were designed to carry) into a chromosome in the human cell. Other viruses, such as adenoviruses, introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome.

- Europe has been a pioneer in the field of Advanced Therapy Medicinal Products (ATMPs) in terms of their development, authorisation, and regulation, thereby supporting patient access to these life-changing therapies. Between Jan. 2014 - Jun. 2019, 323 investigational clinical trials were initiated in Europe. However, this is less than half of what was observed in North America and Asia, with the number of new clinical trials increasing by <2% in Europe versus 36% and 28% in North America and Asia, respectively.

- Industrial Biotechnology:

Genome editing is part of the technology toolbox used in industrial biotechnology for microorganisms used either as production strains in contained use, or in a live form. Due to the precision and ease of genome editing, all genetic engineering work is transitioning rapidly from the older "cloning" techniques to state-of-the-art genome editing techniques, be it for single base substitutions or the introduction of entire heterologous genes. Genetically Modified Microorganisms (GMMs) are widely used in the manufacturing of everyday products and pharmaceuticals; for instance, enzymes are used in a wide range of applications in the food, feed, biofuel and detergent industries. Gene technology is for example being used to develop new enzymes. It is a matter of fact that for some, genome editing is already now the norm rather than the exception.

- Plant Biotechnology:

When it comes to NGT-derived plants, our member companies have focused their R&D efforts on other parts of the world. This is in line with the members' decision adopted for transgenic crops several years ago to focus on other continents, particularly North and South America, due to the dysfunctionality of the EU's authorisation process for cultivation of GM crops. Without a favourable reform of the EU's partly dysfunctional regulatory environment, it is likely that very few NGT-derived plant products will be imported into the EU, and that none will be developed and/ or cultivated in the EU. The EU will fall even further behind many other countries, and consequently miss out on many of the socio-economic and environmental advantages expected from NGT-derived products – just as the EU has already missed out on most advantages from transgenic crops. (For studies proving the benefits of transgenic crops, see CLI benefits database: https://croplife.org/plant-biotechnology/benefits-2/)

- Please see the details provided in section B, questions 10-11.

*** 2. Have your members taken or planned to take measures to protect themselves from unintentional use of NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide details

Our member companies do not unintentionally develop or place on the market NGT-derived products. Our member companies use their established stewardship and quality systems to comply with applicable legislation (including, in this case, legislation relating to laboratories, field trials, or market release for import, processing or cultivation in the EU). As part of these stewardship and quality systems, there is regular information exchange between suppliers and their customers about the compliance of products in the relevant jurisdictions, including whether products fall under the GMO legislation of any relevant jurisdictions.

* 2 bis. Have you encountered any challenges?

- ○ Yes
- ◉ No

* **3. Are you aware of initiatives in your sector to develop, use, or of plans to use NGTs/NGT-products?**

- ◉ Yes
- ○ No
- ○ Not applicable

* Please provide details

- Please find attached (att. 1) a list with several hundred NGT-derived or viral vector related products and research projects, the majority of which are developed by entities (e.g. research institutes, SMEs) other than EuropaBio member companies. (Available online here: and here https://www.europabio.org/cross-sector/publications/genome-edited-products-and-projects-resources-and-examples)

- Healthcare Biotechnology:

In medicine, the growing success of gene therapy has been driven by improvements in viral gene transfer vectors through established techniques (e.g. recombinant techniques) and more recently with the application of NGTs. This development will continue. The European Medicines Agency anticipates up to 20 new applications for EU authorisation of advanced therapies until the end of 2021. The number of new clinical trials has grown by 32% over a 4-year period in 2014-2018 on a global scale, but not in Europe, where the number remained stable. Against this background, it is noteworthy that the biopharmaceutical sector has intensified its R&D activities for in vivo applications of CRISPR/Cas9, which will not be in scope of the NGTs as qualified by this study/questionnaire.

- Industrial Biotechnology:

Genome editing techniques are used to improve microbial strains for the production of food and feed additives and processing aids. Such improvements may include: (a) the targeted deletion of genes that are of potential safety concern (such as antibiotic resistance genes or genes involved in mycotoxin biosynthesis); (b) the targeted duplication/multiplication of intrinsic genes of an organism, to increase production of, e.g., amino acids, vitamins, or other compounds of interest; or (c) the targeted introduction of a (heterologous) gene from another organism, to allow sustainable production of human or animal products (such as human milk oligosaccharides or bovine chymosin).

- Plant Biotechnology:

The multinational agri-tech companies, most of which are EuropaBio members, account for only a small proportion of the developers of NGT-derived plants. However, all are very active in R&D using NGTs for both, enabling innovative plant breeding as well as towards product development depending on market and regulatory oversight. Details are provided in section B, questions 10-11.

- Attachment 1: list with several hundred NGT-derived products and research projects. (Available online here: https://www.europabio.org/cross-sector/publications/genome-edited-products-and-projects-resources-and-examples)

* **4. Do you know of any initiatives in your sector to guard against unintentional use of NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide details

See our reply to question 2.

* 4 bis. Are you aware of any challenges encountered?

- ( ) Yes
- (●) No

*

5. Are your members taking specific measures to comply with the GMO legislation as regards organisms obtained by NGTs?

Please also see question 8 specifically on labelling

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please describe the measures and their effectiveness including details on the required financial, human resources and technical expertise

EuropaBio members are committed to complying with all the applicable legislation, including the CJEU's interpretation that products of genome editing fall under the scope of the EU's GMO directive.

Our member companies use their established stewardship and quality systems to comply with applicable legislation (including, in this case, legislation relating to laboratories, field trials, or market release for import, processing or cultivation in the EU). As part of these stewardship and quality systems, there is regular information exchange between suppliers and their customers about the compliance of products in the relevant jurisdictions, including whether products fall under the GMO legislation of any relevant jurisdictions.

Healthcare and Industrial Biotechnology: NGT-derived microorganisms for contained use in production facilities (mainly for industrial and healthcare biotech applications) are handled like transgenic microorganisms, and the facilities comply with the relevant legislative provisions.

Healthcare Biotechnology:
The EU's Advanced Therapy Medicinal Product (ATMP) Regulation (1304/2007) details specific registration considerations for ATMPs that comprise somatic cell therapy medicinal products, tissue engineered products, and gene therapy medicinal products consisting of and/or containing GMOs. As for any new medicine, well-designed and adequately controlled clinical trials to demonstrate the safety and efficacy of ATMPs consisting of or containing GMOs must be conducted prior to their approval. However, due to their GMO status, these products require additional steps in the clinical trial authorisation procedure. For each clinical trial application, there are three levels of review, which are often performed by separate national agencies:
1. Standard review of a Clinical Trial Authorisation (CTA) application, regulated under Directive 2001/20/EC, which in the EU is a national Member State responsibility (although this will change with the revised Clinical Trials Regulation which is pending entry into force).
2. Ethics review, through which specific issues relating to the use of the GMO are commonly assessed. EU Member States normally assign this review to national or regional agencies with specialist expertise in gene therapies.
3. Additionally, and specifically for products consisting of or containing a GMO, a review of the environmental and biosafety aspects of the use/release of the GMO.

Industrial Biotechnology:
Generally, products produced with GMMs are not GMOs as the production organism is not present in the final product. The production is done in contained facilities. Therefore, regulatory oversight of the use of GMMs for such products is covered by Directive 2009/41 (on contained use) rather than Directive 2001/18 (on deliberate release). Live microorganisms are also used for a variety of products such as yeast for baking, lactic acid bacteria for yoghurt, bacteria for feed use and microorganisms added to the soil in agriculture as alternatives to chemicals. In Europe only non-GMMs are used for these purposes, but classical mutagenesis is often used to remove genes of concern like antibiotic resistance genes. Microorganisms with mutations introduced by genome editing need to fulfil the same requirements as GMMs.

Plant biotechnology:
To our knowledge, no application for market authorisation of an NGT-derived plant has been submitted in the EU. EuropaBio member companies constitute only a fraction of the many organisations (including public research institutions and medium sized companies) which are conducting research and developing NGT-derived plants. In addition, the EuropaBio member companies generally do not import plant commodities, but apply for authorization to facilitate international trade..
We expect that, in the coming few years, no or very few applications for authorisation of NGT-derived plants will be submitted in the EU. This is due to the inefficiency and partial dysfunctionality of the EU's GMO authorisation system, and because the regulatory requirements on detection methods may not be possible to fulfill (See our answer to question 7 for details).
Subjecting all plant products developed with the use of NGTs to the GMO authorisation system will present a formidable hurdle for applicants. The EU's approval system for GMOs is one of the slowest and most unpredictable in the world. The regulatory requirements and costs for the applicant have significantly increased over the years. We estimate a cost of EUR 11–16.7 million for an import GMO authorisation. The average time from submission to an import authorisation is around 5-6 years. (Att. 2, also online https://www.europabio.org/agricultural-biotech/publications/pricing-innovation-out-eu)

* What best practices can you share?

See above

* 5 bis. What challenges have you encountered?

One of the main advantages of using NGTs is that they can make the breeding process much more efficient. However, this advantage is lost if the products have to face 5-6 years of regulatory delay before being put on the market. In addition, the GMO data requrements are highly disproportionate to the level of risk of some NGT-produts (especially these that are similar to products of conventional breeding) and introduce a distorting and onerous burden to their developers. For all products, EuropaBio recommends proportionate requirements, and case-by-case and fit-for-purpose risk assessment.

* **6. Has your organisation/your members been adequately supported by national and European authorities to conform to the legislation?**

- ○ Yes
- ◉ No
- ○ Not applicable

* What challenges have you encountered?

It is currently difficult to conform, at least for certain groups of NGT-derived products. In the case of healthcare biotechnology, there is considerable fragmentation due to diverging national interpretation of EU legislation.

Healthcare Biotechnology:
In medicine, there is significant clinical trial complexity in the EU owing to Member States own interpretation of Clinical Trial Authorisation legislation. In the case of Advanced Therapy Medicinal Products (ATMPs) consisting of or containing GMOs, an additional approval for the environmental and biosafety aspects of the use and release of the GMO is required by the GMO competent authorities who often operate independently of the health authorities. Local interpretation of GMO legislation that was not developed specifically for medicinal products has resulted in highly fragmented procedures across the EU in terms of the classification,

requirements and timings for GMO applications and approvals. As such, developers have found adherence to the GMO legislation as resource intensive and confusing with little apparent patient, product or environmental benefit. Additionally, several rounds of reviews can result in delays of up to 12 months to planned CTAs in some cases. Without action, these barriers can disincentivise ATMP developers to conduct trials in the EU with ATMPs consisting of or containing GMOs, affecting patients and EU competitiveness. The upcoming Clinical Trial Regulation (CTR) (EU) No 536/2014 aims to promote the implementation of a harmonised CTA dossier and review timelines adopted by all Member States. However, EuropaBio is concerned that ATMP products will fall out of the CTR process owing to unrealistic review and response timelines as well as a submission portal that is not fit for purpose for ATMPs.

Industrial Biotechnology:
The industrial biotech sector did not see a reason nor a rationale why to ask for support by authorities to conform to the current, outdated GM legislation (as applied to genome editing). Instead, what it asks for is commitment, dedication and support to make a future legislation fit-for-purpose. We expect such future legislation to be science-based, risk-proportionate, and product-centric (instead of the current process-centric approach).

Plant Biotechnology:
The support of national competent authorities in the EU regarding questions related to the use of NGTs has been limited, because the decisions how these products are regulated and the application of the regulatory system are (mostly) done at the EU level. The application of GMO legislation has been poor and inefficient, especially when it comes to the dysfunctional system for cultivation, as detailed in several of our other responses. A number of member states have been unsupportive by 1) voting against the authorization of GM crops despite them having been assessed to be at least as safe as conventionally bred crops, and by 2) banning on their territories the cultivation of the only GM crop approved for cultivation in the EU.
Furthermore, it would be extremely challenging for developers of NGT-derived plants which could also have been obtained through earlier breeding methods or resulted from spontaneous processes in nature to submit a complete dossier for authorization in the EU, including a detection method, as confirmed by the EU Commission's Joint Research Centre in their report. See our answer to question 7 for details.

* **7. Does your sector have experience or knowledge on traceability strategies, which could be used for tracing NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please describe the traceability strategy, including details on the required financial, human resources and technical expertise

Full reply slightly over limit - att. 3. Below = slightly abbreviated. "GE" = "genome edited"

The traceability of NGTs will be one of the biggest challenges in terms of compliance with the current GMO legislation. Companies use their stewardship & quality systems to comply with legislation and exchange information about the products they buy and sell. Traceability would be much easier to guarantee if the legislation focused on the properties of organisms more than on the technologies used to make them.

Health:
Traceability requirements as applicable for medicinal products will be followed for medicines based on NGT-products. Most notably, Reg. 1394/2007 Art 15, requiring the submission of a risk management plan has to be submitted in accordance with the current EU legislation and pharmacovigilance guidelines. Track & trace

systems for individual products which keep the collected data for 30 years are also required. In addition, the Guidance EMEA/CHMP/GTWP/60436/2007 and the Guideline on GMP for ATMPs Vol IV para IV C(2017) 7694 provide for additional recommendations on traceability. Therefore, additional traceability strategies will not be necessary since viral vectors and genetically modified human cells are incapable of replication or long-term survival in a release environment.

Industrial:
Companies have a traceability system already in place, namely the quality system they use to secure that their products are fully compliant with applicable legislation. As part of these systems, there is regular information exchange between suppliers and their customers about the compliance of products in the relevant jurisdictions, including whether products fall under the GMO legislation of any relevant jurisdictions.

For contained use microorganisms, there is no need for traceability since they remain in the production premises. Still for fermentation products for food and feed purpose there is a requirement for residual DNA analysis that is specific for a specific GMO. For live microorganisms, we could think of the following strategies:
Microorganisms that have been modified in ways that are analogous to transgenesis could be subject to documentary traceability. In addition to this, there would be the possibility to perform an analytical traceability, based on the microorganism's single genetic characteristics that were described by the applicant when applying for authorization for deliberate release. The latter option would however require significant resources and technology at control laboratories.
Microorganisms that cannot be distinguished from counterparts made with traditional techniques or even natural counterparts are more challenging to track. Paper tracing may be possible to some extent for such microorganisms.

Plants:
We are not aware of an effective, enforceable traceability system that could be used for detecting NGT products. Approaches to fulfil traceability requirements would be highly challenging to implement for commodities.

As part of the GMO authorisation, methods for detection & identification need to be provided & consequently validated by EURL. GMO detection methods (DM) are based on the identification of a specific transformation event. Some GE plants have genetic changes that could also have been obtained through earlier methods or nature. Hence, approaches used for GMOs can not always be applied to NGTs.

In many cases, it may be impossible to distinguish if a mutation was achieved by a particular mutagenic method or a natural process. We concur with ENGL (Att 4 & https://bit.ly/2y5fxtz): GE plants cannot be detected with the current GMO screening strategies & it is questionable if event-specific identification & quantitative DMs can be developed for all NGT plants. DMs for plants with non-unique DNA alteration will probably lack the specificity required. Accurate quantification may be challenging for minute changes. ENGL concludes: validation of an event-specific detection method & its implementation for market control is not feasible for NGT plant products carrying a DNA alteration that is not unique.

For the purposes of detection & identification, applicants are required to develop a unique identifier (UI; Reg. 1830/2003) for each GMO. If NGT products are classified as GMOs, this requirement would apply even when the resulting product does not carry a novel combination of genetic material. Assigning a UI to such products would contradict the approaches of several countries (incl. Chile, Brazil, Colombia) to treat such products as conventional products, not covered by their GMO laws (ie no OECD UI needed). The inclusion of NGT products in the same OECD product database and with the same identification principles as used for GMOs would disseminate incorrect information about the genetic makeup of genome edited products and

create confusion among stakeholders. Only if NGTs are used to generate transgenic plants, the UI should be assigned.

* **8. Are your members taking specific measures for NGT-products to ensure the compliance with the labelling requirements of the GMO legislation?**

- ○ Yes
- ◉ No
- ○ Not applicable

* Please describe the measures and their effectiveness including details on the required financial, human resources and technical expertise

The EuropaBio member companies are committed to adhering to all applicable legislation.
The labelling requirements in the case of medicinal products consisting of or containing GMOs are defined by the pharmaceutical legislation.
There are currently no NGT-derived plants on the EU market, to our knowledge. Generally, products produced with/by GMMs (genetically modified microorganisms) fall under Directive 2009/41/EC on the contained use of microorganisms. There is no GM labelling requirement for these. See also our reply to Q5, as well as section G on labelling.

* What best practices can you share?

-

* Please explain why not

-

* 8 bis. What challenges have you encountered?

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* **9. Do you have other experience or knowledge that you can share on the application of the GMO legislation, including experimental releases (such as field trials or clinical trials), concerning NGTs/NGT-products ?**

- ◉ Yes
- ○ No
- ○ Not applicable

* Please describe for the:

- ☑ Agri-food sector
- ☑ Industrial sector
- ☑ Medicinal sector

Agri-food sector

The application of the GMO legislation has many deficiencies, as confirmed regularly since 2004 by studies mandated by the European Commission. For example: “Study – Means to improve the consistency and

efficiency of the legislative framework in the field of biotechnology" (2004), and the two reports on the evaluation of the GMO legislation published in 2011: https://ec.europa.eu/food/plant/gmo /reports_studies_en. These reports recommended, inter alia, for the Commission and EFSA to keep to the legally foreseen timelines, for the risk assessment procedure to be streamlined (notably regarding stacked events), and they highlighted the need for reasonable thresholds (rather than a zero tolerance policy). One of these two reports stated clearly that Directive 2001/18, as currently implemented is not fit for purpose. It also stated: "The procedures for the risk assessment for GMOs as implemented are not efficient, time-limited or fully transparent"".

Plant Biotechnology:
While we do not have direct experience with the application of GMO legislation to NGT-products, we have extensive experience with how the EU administers the regulation for transgenic GMOs and we are concerned that a similar situation will occur in the handling of NGT-products, should any developer attempt to enter the EU authorization process in its current form.

- The plant biotechnology member companies have moved almost all their field research and development of transgenic plants out of the EU, and their efforts are now focused on other continents.
- The bureaucratic implications, associated costs, lengthy risk assessment and a lack of predictability as to the approvals create very significant hurdles for any potential applicants and have strongly discouraged public researchers and private companies from developing GM or NGT-crops in and for Europe.
- In 2002, Commissioner Busquin communicated in a Commission press release that 'field research on genetically modified crops has virtually come to a halt in most EU countries', with a total of 88 notifications at the time. Between 2010 and 2016, the number of GMO field trials in the EU declined by about 90%, and many of the remaining field trials were destroyed by activists. In 2020 so far, 2 notifications for field trials can be found on the Commission's JRC website.
- Only one GMO product is approved for cultivation for commercial purposes in the EU and the vast majority of cultivation applications were withdrawn around 2012-15. The remaining few cultivation dossiers have been repeatedly positively assessed by EFSA. However, they have been waiting for Commission approval for years now, whereas the EU Ombudsman decided that 3.5 months is already maladministration at this final stage of the procedure (Ombudsman complaint 1582/2014/PHP).
- The Commission has in many cases failed to put the cultivation dossiers to the vote by Member States, despite the legal obligation to do so within 3 months of publication of the EFSA scientific opinion. The Commission's failure to fulfil its obligations was confirmed by the EU's General Court, which ruled that "the European Commission has failed to fulfil its obligations (…) by failing to submit to Council" a GM dossier and added that "the Commission cannot, in a dilatory manner, repeatedly request opinions from EFSA". (Judgement in Case T 164/10).
- Directive 2015/412 ("GMO opt out directive") allowing Member States to ban cultivation of authorised GMOs on their territory has reduced certainty and potential cultivation even more.
- No new application for GM cultivation has been submitted for years, and EuropaBio members are now focusing their GM cultivation product pipelines on other parts of the world.
- Also, the Group of Chief Scientific Advisors of the European Commission stated that: "meeting the obligations of the GMO Directive implies cost and a long duration of the approval process, which are difficult and onerous to bear, particularly by small and medium enterprises". https://ec.europa.eu/info/sites/info/files /2018_11_gcsa_statement_gene_editing_1.pdf

Industrial sector

Industrial Biotechnology
For industry sectors that focus on contained-use applications of biotechnology (i.e., fermentation; e.g. food and feed additives and processing aids), this question does not apply.

Medicinal sector

Healthcare Biotechnology:
In medicine, Advanced Therapy Medicinal Products (ATMPs) that consist of or contain GMOs are required to undergo additional approval procedures by GMO competent authorities in each Member State prior to clinical trial authorisation (CTA). This regulatory framework was not designed for pharmaceuticals and is not standardised across Member States resulting in developers undergoing multiple, inefficient and redundant procedures which are costly and can lead to significant delays to development programs. A single, networked approach conducted in parallel to CTA assessments is desired with the upcoming Clinical Trials Regulation providing an opportunity for the EC to work with GMO authorities to achieve this. EuropaBio would like to collaboratively explore with the EC whether GMO requirements are appropriate for medicines given the current state of knowledge as well as how duplication between some medicines and environmental agencies can be avoided to ensure streamlined processes are in place to handle the increasing number of these products under development. See also attachments 5 & 6.

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

The maximum file size is 1 MB

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B - Information on research on NGTs/NGT-products

* **10. Are your members carrying out NGT-related research in your sector?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify including subject, type of research, resources allocated, research location

Yes, many if not most of the member companies of EuropaBio and of the national biotechnology industry associations are carrying out NGT-related research, especially using genome editing techniques. All of our member companies active in plant breeding and agricultural biotechnology are carrying out such research, as well as the majority of our healthcare member companies and a sizeable number of our member companies in industrial biotechnology.

For reasons of the protection of intellectual property our members cannot disclose the subject, type of research and resources allocated. One can simply assume that this concerns all fields of application of biotechnology.

One of the main advantages of using NGTs is that they can make the breeding process or microbial strain

development process much more efficient.. However, this advantage in R&D would be lost if the products then would have to face years of regulatory delay before being put onto the market. In addition, the potential markets for many products are small compared to the regulatory investment which would be required to place these products on the market, i. e. it is entirely impossible to recoup investments in these cases.

Despite these difficulties, we are aware of several hundred examples of genome editing applications by public and private innovators. Eleven “What if” examples from the different biotech sectors are currently listed on our EuropaBio website section on genome editing: https://www.europabio.org/priority/genome-editing. In addition, we have listed 150+ concrete examples in annex 1 (same document also annexed to our replies to Q3 & Q11, also available online https://www.europabio.org/cross-sector/publications/genome-edited-products-and-projects-resources-and-examples). Our guess is that the real number, including company pipelines all over the world, is much larger than 1000.

Many of the innovative projects in an organisation’s pipeline are ultimately not brought to market, inter alia when it turns out that there is no feasible path to generate return on investment.

Healthcare biotechnology:
In medicine, 2019 was a significant year of growth for the advanced therapies sector in Europe. There were 260 ongoing advanced therapy medicinal product (ATMP) clinical trials involving the vast majority of EuropaBio biopharmaceutical member companies. At EuropaBio, more than 50% of member companies are active in advanced therapies.

Industrial Biotechnology:
In the fermentation industry, for targeted improvement of production strains, genome editing is already now the norm rather than the exception, and is used to make improvements to such strains as outlined in the answer to Q3. R&D is done also in the EU.

Plant Biotechnology:
This is especially the case when the path to market includes lengthy, expensive or even unpredictable authorization processes, such as the EU’s GMO authorisation process, which currently applies also to genome edited organisms, and which makes very many potential innovations economically unfeasible for the EU market.

*** 11. Are you aware of other NGT-related research in your sector?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify

Yes. Researchers in public and private institutions across Europe and the globe have embraced genome editing and other NGTs because they are more precise, efficient, versatile and provides ample opportunities to develop new and improve existing processes and products in the areas of healthcare, the bioeconomy, and food & feed. Accordingly, we estimate that there are thousands of examples of research, if we include basic research.
The number of academic publications and patent filings has exploded over the last few years.
We have listed 150+ concrete examples in the annex 1 (same paper also annexed to Q3 and Q 10., also available online: https://www.europabio.org/cross-sector/publications/genome-edited-products-and-projects-resources-and-examples)

Healthcare Biotechnology:
In medicine, there are more than 240 companies across Europe developing ATMPs. The total financings by European-based biopharmaceutical companies in 2019 was 2.7 B Euro.

Industrial Biotechnology:
Genome editing techniques are the norm rather than an exception for those doing targeted improvements of production strains in the fermentation industry. If one can choose between the use of old-fashioned GMO techniques, vs. the use of state-of-the-art, precise genome editing, what would be the rationale for staying with the old-fashioned approach, if both fall under the same regulatory approach?

Plant Biotechnology:
On CRISPR technology in plants alone, JKI counted close to 1000 scientific publications by early 2018, most of which came from China (541) and the USA (387), followed by Japan (87). In the same publication, JKI also lists 102 publicly accessible applications submitted prior to May 2018 which, according to JKI, can be characterised as covering 'market oriented' or 'ready for market' products developed through gene editing. See JKI 2018 (p. 5): https://www.bmel.de/SharedDocs/Downloads/Landwirtschaft/Pflanze/GrueneGentechnik/NMT_Stand-Regulierung_Anlage4-Aktualisierung.pdf?__blob=publicationFile

For the wider plant breeding sector, the vast majority of companies, including small and medium ones, are conducting research with NGTs. Our partner association Euroseeds will provide more detail on this.

* **12. Has there been any immediate impact on NGT-related research in your sector following the Court of Justice of the EU ruling on mutagenesis?**

Court of Justice ruling: Case C-528/16 http://curia.europa.eu/juris/documents.jsf?num=C-528/16

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please describe

Yes. Together with Europe's scientific community, we regret that implementation of this ruling could cause European life science innovation effectively to come to a halt, as stated in EuropaBio's statement on the court ruling:
(Att. & https://bit.ly/3cBB3oF). Please find this reply with hyperlinks to sources in Att. 8.

We know of many examples of companies & public research organisations which have given up on their plans to bring genome edited products to the EU market for the foreseeable future, for example because public research grants were stopped in response to the court ruling.

As stated in our statement on the court ruling, "If fast mitigation is not done, the ruling will cause a halt to EU sustainability and competitiveness ambitions by hindering the delivery of innovative bio-based products to the market, sustainable innovative food-solutions and certain healthcare solutions to patients," all the more since "the EU has already fallen far behind the rest of the world in this essential area".

Industrial Biotech:
The CJEU ruling emphasized the fact that the technology-based approach of Dir. 2001/18 is obsolete considering the innovation rate in modern biotechnology. Subsequent debates around the ruling made it clear that it would take a lot of efforts to modernize the legislation and facilitate global trade. This led to debates in the industrial biotechnology sector on whether it was still worth keeping R&D facilities and jobs in the EU, and developing and placing innovative products on the EU market. There was no immediate impact

on the running business, as no NGT-derived product was developed and/or placed on the EU market under the assumption that it can be considered a non-GM product in the EU. Nevertheless, the ruling did have an immediate negative impact on innovation by preventing the pursuit of innovative concepts that would have benefitted both the conventional and non-GM markets. For some products intended for non-GM applications, industry needed to switch back to classical mutagenesis rather than using more appropriate genome editing approaches. In summary, the ruling prevented the use of innovative approaches of genome editing in some markets. One example is the potential use of genome editing in generating bacteriophage-resistant dairy cultures (Börner et al., FEMS Microbiol. Lett. 366:fny291, 2019; Stuer-Lauridsen & Janzen, European Patent No. EP 1 838 839 B1). As dairy cultures are traditionally a non-GM business, the “GM classification” of such phage-resistant strains plays an important role in determining market access and market success.

Agriculture technology companies voice intention to move R&D abroad: KWS seed company and HZPC, a Dutch trader in seed potato, confirmed that they will have to move part of their R&D outside Europe. The Dutch plant breeders’ association Plantum confirms: ‘As long as the new methods fall under the GMO legislation, companies based in the Netherlands will not invest in them, which puts their strong position in the global market at risk.” According to Reuters, several agri-tech multinationals ‘all but ruled out pursuing genetic plant breeding at home after the EU (ruling)’.

Research assignments are being withdrawn, reports Wageningen UR. In some Member States, public researchers reported an almost immediate cut of research funding for projects related to gene-edited crops, following the court ruling. In the majority of the (few) cases where field trials with gene-edited crops are taking place, these have been immediately required to come into compliance with GM legislation or preliminary decisions to regard those plants as non-GM plants were withdrawn.

Companies lose financing and put projects on hold: According to Nature, a Belgian start-up that planned to use CRISPR technology to help Africa’s banana industry says it lost its financing, while a company in Brazil says it has put millions of dollars’ worth of gene-editing projects focused on soya beans on hold because its major market is in Europe.

Paradoxically, the EU has itself funded a wide range of research projects which involve CRISPR-Cas applications in e.g. agriculture and healthcare through several of its programmes (I.a. Horizon 2020, FP7, FP6, FP5 or the European Research Council). Within the agricultural scope alone, the total of these EU investments amounts to nearly € 27 million for 22 projects. For 148 projects related to healthcare applications, this even amounts to nearly € 197 million. With the CJEU ruling bringing these techniques under the umbrella of Directive 2001/18, institutions and companies in the EU are unlikely to reap the benefits of these tax-funded research projects.

Healthcare biotech:
Most of the clinical trials with medicinal products using NGTs (mutagenesis) techniques were initiated after the Court of Justice of the EU ruling on mutagenesis. Sponsors of these clinical trials comply with the GMO requirements as for any other gene therapies.

*** 13. Could NGT-related research bring benefits/opportunities to your sector/field of interest?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide concrete examples/data

Yes, see our reply to Q 16. Scientific research adds important contributions to humanity's pool of knowledge, and basic research continues to enable scientific and technological breakthroughs, including on genome editing. Concrete benefits and opportunities tend to arise from applied research that leads to concrete solutions, usually in the form of products for the marketplace, which could contribute to more diversity and competition on the seed markets. This is why we provide a more detailed reply to the overlapping but – in our view – more relevant Q 16.
For industrial biotechnology, as already outlined in the answer to Q3, potential benefits/opportunities may include the targeted deletion of mycotoxin gene clusters (or other sequences of potential safety concern); the targeted deletion of sequences contributing to strain instability, thereby securing even better consistency in product quality; or the targeted deletion of antibiotic resistance genes (some microorganisms intrinsically contain such resistance genes). In addition, competing pathways resulting in unwanted side products in the final commercial preparation may be deleted in a targeted manner.
In healthcare biotechnology, advanced therapies have ground-breaking therapeutic potential, particularly in disease areas where treatment options are absent or inadequate. Excitingly, these therapies are starting to potentially allow us to cure challenging conditions with a one-off treatment. As a result, they have significant benefits for families, society and healthcare systems.

*** 14. Is NGT-related research facing challenges in your sector/field of interest?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide concrete examples/data

Yes. With the preliminary CJEU ruling interpreting that NGT-derived organisms should, in general, be regulated like transgenic organisms in the EU, numerous company R&D programmes have been shut down or moved outside the EU and some public research project have equally been shut down or are threatened by the withdrawal of funding. (see our reply to Q 12).

Healthcare biotechnology:
In medicine, as outlined in previous replies, without action to optimize the clinical trial authorization process, the existing barriers can disincentivise ATMP developers to conduct trials in the EU with ATMPs consisting or containing GMOs, affecting EU patients and EU competitiveness.

Industrial biotechnology:
Microorganisms with mutations introduced by genome editing need to fulfil the same requirements as genetically modified microorganisms (GMMs).This may discourage the biotech industry from research / investing in genome-edited microorganisms for sectors such as food, feed, bioag, bioremediation.
The most significant and impactful challenge is the regulatory burden linked to commercializing products obtained through NGTs, dependent on the applicable regulatory framework, including the challenges of non-harmonized regulatory systems in different countries, with a product obtained by genome editing potentially being considered "GM" in one country, but "non-GM" in another country. If the regulatory system is not adequate and risk-proportionate, and fails to deliver the needed legal certainty, it will act as a roadblock to investment in promising approaches to address the global environmental, health, and socio-economic challenges that this planet is facing.

Plant biotechnology:
The CJEU ruling extends the partly dysfunctional EU GMO authorisation system to NGTs.
EuropaBio's statement on the court ruling (https://www.europabio.org/sites/default/files /EuropaBio_statement_CourtRuling_final_forWEB.pdf) includes this paragraph:

"The EU's approval system for GMOs has prevented farmers from accessing products that have been used safely for decades in other parts of the globe and is so slow and expensive that even import authorisations represent an insurmountable hurdle for small and medium-sized companies and public institutions. Yet it is exactly these SMEs and publicly funded innovators who have the biggest share of genome edited organisms ready to offer to the market and will now likely be unable to do so in the EU. The result is that they will instead focus their research on other parts of the world, where these organisms are usually not treated like genetically modified organisms."

The GM authorization system takes ca. 5-6 years on average and costs the applicant an estimated 11 to 16.7 million EUR for import authorisations only and has proven to be dysfunctional when it comes to making GM crops available to farmers in the EU for cultivation purposes. Only very few companies in the world can afford and manage to apply for food and feed processing and import authorisation. However, none have applied for EU cultivation authorisation in recent years. The products that can generate a return on investment have to be blockbuster traits in widely grown crop types, which have the potential to be grown by hundreds of thousands or millions of farmers.

* **15. Have you identified any NGT-related research needs/gaps?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify which needs/gaps, explain the reasoning and how these needs/gaps could be addressed

Yes. As for every single discipline of science, there is always a need and desire for additional research. This is why so many research programmes and projects are ongoing (see previous replies), and this is also why the EU has funded well over 150 NGT related research projects with over 226 million EUR (see our list of genome-edited products and research projects attached to several of our replies). Humans have been adapting the genomes of other species for over 10,000 years, starting with the domestication of plants and animals. The outstanding progress in the life sciences and genetics means that today we understand almost a lot more about genes than a few decades ago. In the second half of the 20th century, conventional breeding of different species including plants and micro-organisms was facilitated by provoking many random mutations that increased the genetic variability above what would occur under selective breeding alone. Then, by trial and error, new variants which showed desirable traits were identified and selected for further breeding. In contrast, the precision of genome editing allows for the cteation fo desirable genetic variation for specific traits, with very minute changes, if any, outside of the desired target region. The achievement of such precisionrequires prior sequencing and detailed basic research on the genomes of the species which are being edited. There is much left to do to expand our knowledge of genomes to more species. For example, intensive efforts to map the wheat genome have been going on since (at least) 2004. Another field of interest concerns next generation NGTs.

In the area of human genome editing, it is crucial that the global community, involving government, academia, industry, and society at large, joins efforts to research the technical, scientific, medical, legal, societal, and ethical issues associated with genome editing of human germline cells and embryos, with a view to establishing an international governance framework. It is also highly desirable that the international community of bioethicists steps up the research on the ethical dimensions of germline genome editing.

Industrial biotechnology: For use of genome editing in R&D to develop commercial products (in the food and feed industry; i.e. primarily working with safe microorganisms), two important aspects are worth mentioning: (a) the intrinsic higher precision and accuracy of state-of-the-art genome editing approaches to achieve a

desired improvement of a strain as compared to earlier approaches of genetic engineering; and (b) the availability and ease of whole-genome DNA sequencing to confirm that the strain improvements have occurred as planned and that no additional sequences were changed. These two aspects, taken together, lead to the conclusion that there are no additional risks on top of those already considered and assessed for earlier approaches of genetic engineering, and that the current risk assessment framework can also be applied to assess products obtained with genome editing.

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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42a8cbbd-ce56-49ec-8952-2f4c2d14fadd/8_Q12_reply_with_hyperlinks.pdf

C - Information on potential opportunities and benefits of NGTs/NGT-products

* **16. Could NGTs/NGT-products bring benefits/opportunities to your sector/field of interest?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Yes. The reason why well over 150 genome edited products have been developed is that they bring benefits, opportunities and solutions. The reason why researchers choose to use genome editing and other NGTs to develop these products is because NGTs are more efficient and precise than most previous breeding and genetic engineering techniques. Please consult also our list of genome edited organisms (att. 1 and https://bit.ly/2WzVNHG) to see the great variety of traits which have been developed by a large variety of innovators for a large amount of different species.

Healthcare Biotechnology:
In medicine, Advanced Therapy Medicinal Products (ATMPs), the majority of which are NGT-products, have an incredible potential to treat currently incurable genetic diseases, rare conditions and offer durable and life-changing solutions for patients. Some therapies address the root cause of the disease offering patients the prospect of a cure with potentially one intervention only. Cell and gene therapies are sometimes manufactured specifically for one individual patient creating tailored medicine. Currently, ATMPs are developed and/or applied for cancers, such as rare blood & skin cancers, inherited blindness and blindness caused by injury, rare genetic diseases, such as Crohn's disease, epilepsy, Parkinson's disease, Alzheimer's, spinal muscular atrophy, rheumatoid arthritis, diabetes, etc. The healthcare examples EuropaBio has featured in our "What If" factsheets concern targeted cancer treatments, Childhood blindness, sick blood cells and AIDS: https://bit.ly/3dKSSBS

Industrial biotechnology:
The examples EuropaBio has selected for our "What If" factsheets concern algae to make biofuel, enzymes to produce hydrogen peroxide without petroleum, and wood that is transformed into food preservatives: https://bit.ly/3dKSSBS
Microorganisms used in food and feed as cultures/probiotics/silage agents: the genetic basis for e.g. antibiotic resistance can be accurately and easily eliminated. The benefits are an improved use of feed by animals, leading to less use of raw materials and less production of waste.

Microorganisms used in agriculture: several agronomical properties such as nutrient uptake and resistance to heat or draught can be introduced into a single microorganism, which would be much more demanding with “pre-2001” technology. The benefits are an improved use of nutrients and a more consistent yield of crops under challenging climate conditions, without additional use of mineral fertilizers or chemical pesticides. For the potential benefits, see also the answers to questions 3 and 13. These benefits are not specific to NGTs; however, the benefits can be realized with higher precision, higher accuracy, and often through more subtle changes needed to realize a particular, desired effect. In addition, they can be reached with higher technical ease.

Plant biotechnology:
There are well over 150 examples in our list. Genome editing can improve plant varieties in ways that are beneficial to the farmer (disease resistance, better stress tolerance, etc.) or ways that are beneficial to the consumer (improved nutrition, longer shelf life, etc.). For a recent overview of ongoing research on ways to tackle flooding, salinity, extreme temperatures, to reduce fertilizer use etc., please see Bailey-Serres et al, “Genetic strategies for improving crop yields” (Nature, 2019). Some of these improvements can be achieved with traditional breeding, but that takes much longer than with state of the art NGTs. Efficiency is essential, because the challenges are increasing with the need to double food production by 2050 (according to the FAO) on very limited agricultural land, and with a view to climate change (pests move to new areas, weather extremes, etc). The plants EuropaBio has selected for our “What If” factsheets are: gluten free wheat, low acrylamide potatoes and healthier oil soya. These all provide important consumer and health benefits: https://bit.ly/3dKSSBS

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

For a number of products and traits, similar benefits might be achievable also using earlier methods, which would however be less efficient and less targeted.

* **17. Could NGTs/NGT-products bring benefits/opportunities to society in general such as for the environment, human, animal and plant health, consumers, animal welfare, as well as social and economic benefits?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Yes. Please see our reply to the previous question (Q16). Each of the more than 150 genome edited products provided in our list is designed to solve a problem or perform better than a comparable existing product (att. 1 and https://bit.ly/2WzVNHG).

The economic benefits depend mainly on the marketplace, provided that the innovation is allowed to reach it. Since NGTs and NGT products are designed to solve problems and perform better than comparable existing products, they can be used as a tool to address current societal and environmental issues, including those flagged by the Commission as priority issues. For instance, climate change will put additional pressures on the agricultural sector (e.g. increased diseases, unfavourable weather, etc.). Dealing with these challenges will require access to every possible tool for maximum flexibility. Similarly, consumer benefits of NGT

products are not only directly economically beneficial (higher value products can be sold at a higher price) but have wider societal benefits too: a healthier population is more economically beneficial (examples here include nutritional benefits).

Biotechnology would provide even more benefits in Europe, if there was a greater political acceptance and a regulatory framework that secures consumers' and environmental safety, while allowing innovative products to reach the market in a timely and proportionate way.

Healthcare Biotechnology:
In medicine, specifically, ATMPs have transformative impact for patients, families and society. Advanced therapies are driving a growing share of the biotech and biopharma industries development pipeline creating jobs and economic growth, and further developing the knowledge-based economy. ATMPs bear the promise of providing patients with life-long potential cures which will alleviate most of the financial burden in healthcare systems and contribute to their sustainability. ATMPs are currently the only medicinal products enabling the tackling of the genetic root cause of diseases such as rare diseases as well as serious chronic diseases. Where standard medical and surgical practice have not proved effective in curing or treating genetic diseases, advanced therapies emerge as a promising option for a potentially lifelong cure.

Industrial Biotechnology:
Through the precise and targeted deletion of (a) mycotoxin gene clusters (or other sequences of potential safety concern) and (b) pathways resulting in the formation of unwanted side products, the intrinsic safety of production strains used in industrial fermentations, as well as the consistency in final product quality can be further improved. In addition, the use of precise and targeted techniques to improve production strains, combined with whole-genome sequence analysis to confirm the correctness of the targeted mutations will allow to continuously reduce the need for animal experimentation to confirm the safety of fermentation products, thereby contributing to animal welfare. An example of clear-cut environmental benefits is, for instance, the fermentative production of riboflavin (vitamin B2) using genetically engineered production strains. While the current industrial production strains for vitamin B2 were generated using traditional genetic engineering approaches, it is conceivable that further improved production strains can be obtained by genome editing. Vitamin B2 is an indispensable, mandatory component of infant food, and biotechnological production is the most environment-friendly approach to produce it. As already outlined in the answer to Q16, the benefits are not unique to genome editing, but they can be realized with higher precision, using more subtle genetic changes, and with greater ease.

* Under which conditions do you consider this would be the case?

Biotechnology would provide even more benefits in Europe, if there was a greater political acceptance and a regulatory framework that secures consumers' and environmental safety, while allowing innovative products to reach the market in a timely and proportionate way.

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

For a number of products and traits, similar benefits might be achievable also using earlier methods, which would however be less efficient and less targeted.

* **18. Do you see particular opportunities for SMEs/small scale operators to access markets with their NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Healthcare biotechnology:
In medicine, the representation of SMEs in the development of advanced therapy medicinal products (ATMPs) is dominating. SMEs will benefit a lot from the optimization of the GMO requirements for clinial trial authorisations, as well as from better and more accessible financing schemes.

Industrial Biotechnology:
Due to the higher precision and technical ease, use of genome editing technologies does not per se require the same level of expertise and technical equipment (incl. laboratory automation) as often is needed with traditional genetic engineering techniques, where often many individual clones needed to be analyzed in order to find the particular (rare) strain with the desired improvement. This makes the use of genome editing techniques more promising and affordable to SMEs. Certain technologies developed in the last 10 years are less complex or costly to implement than older gene technology tools. This makes them in principle more accessible to SMEs. However the same regulatory obstacles as for larger companies apply (the GMO legislation).

Plant Biotechnology:
Elsewhere yes, but not the in the EU. Relatively small operators are accessing markets outside the EU, but the same almost certainly will not happen with the EU market, as long as all NGT derived products are treated as if they were transgenic products. In the EU, only multinationals have managed to bring GMOs to the market (mainly as commodity imports not for cultivation), due to the extensive, disproportionate data requirements and prolonged timelines compared with other markets. In countries where a vast majority of NGT-derived varieties are deemed not to be transgenic and therefore are considered in the same way as conventionally bred products, most of the developers bringing these products to the market are smaller companies and public research institutions, not multinational companies. For example, as of 6 May, 43 letters of inquiry published in the USDA database 'Am I Regulated', from product developers to find out whether their biotech applications fall under the biotechnology oversignt of the USDA, were made with NGTs. Of those, Only 12 % of the developers are multinational (agri-tech) companies. 46% are medium sized and smaller companies, and 42% are public institutions. See our list (attachment 1 annex 1 and https://bit.ly/2WzVNHG)

* **19. Do you see benefits/opportunities from patenting or accessing patented NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Yes, a strong protection of intellectual property is a necessary precondition to enable innovation, because it increases the chances of the innovator to recoup their investment in the innovation.
Developers of NGTs and NGT-products need an internationally competitive suite of intellectual property incentives and R&D reward mechanisms to ensure continued investment in innovation in various industrial sectors, such as biopharmacy (e.g. rare disease medicines and advanced therapies) and plant breeding (e. g. novel traits)., The EU should strive to enhance the competitiveness of the EU IP system, further incentivising the development of NGT-derived products.

A case study about patented (non-GMO, non-NGT) Ogura rapeseed in France highlights that € 1 billion societal benefits accrued during the Ogura patented life, of which 75% of societal benefits accrue to farmers and consumers. Despite this huge success, it took the innovator (INRA, the French national research institute for agriculture) 15 years to obtain break-even point. See attachment 7 and https://www.europabio.org/cross-sector/publications/who-benefits-ip-rights-agricultural-innovation-0. Similarly, the more entities are able to access the available NGT (e.g. through licensing) the bigger the chance that innovative products will be developed.

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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D - Information on potential challenges and concerns on NGTs/NGT-products

*** 20. Could NGTs/NGT-products raise challenges/concerns for your sector/field of interest?**

- ○ Yes
- ◉ No

* Please explain why not

We do not associate any particular challenges or concerns with the use of genome editing techniques and for commercial products developed with such techniques, when compared to those derived from more traditional techniques of genetic engineering. The most significant challenge and concern is the potential regulatory burden, dependent on the future regulatory framework for biotechnological products. An overly demanding regulatory framework to obtain market authorizations and to comply with post market requirements including labelling and traceability needs, will risk to seriously stifle innovation in this field by delaying or entirely keeping NGT-products off the EU market. In healthcare biotechnology, more specifically, the expected rise in the number of applications with gene therapies is likely to create resource difficulties which may have knock-on effects on approval timelines and enrolment of patients in clinical trials.

EuropaBio takes ethical concerns regarding germline genome editing in humans seriously (see our reply to Q 26).

Plant Biotechnology:
Despite the current lack of international harmonisation as regards regulatory approaches to NGT products, many third countries follow the principle that only products with a novel combination of genetic material as laid out in the LMO definition of the Cartagena protocol on Biosafety are in the scope of GMO regulations (e. g. “Stable insertion into the plant genome of one or more genes or DNA sequences that are part of a defined genetic construct”).
This includes important agricultural countries in North and Latin America which consider NGTs as conventional crop varieties. Very few jurisdictions (such as New Zealand) subject NGT-derived products fully to the rules for transgnenic products, as the EU does.

Different requirements worldwide would reduce and slow down the capacity of the industry to innovate, limit the diversity of genetic resources, have a negative effect on research collaborations, and hinder the movement of germplasm and seed globally. In addition, commodity trade disruption will easily occur, and agricultural development and food security will be impeded.

The challenge of trading NGT products (this could be commodities and seeds) was recognized also by the WTO. In a statement “Agricultural Applications of Precision Biotechnology”, eight countries mention that differing domestic regulatory approaches for products derived from precision biotechnology may result not only in internationally asynchronous approvals, but also in asymmetry of regulatory approaches, and create potential trade issues that could impede innovation. They call upon governments to exercise due consideration to avoid arbitrary and unjustifiable distinctions between end products derived from precision biotechnology and similar end products obtained through other production methods. (WTO Statement 2018 Agricultural Applications of Precision Biotechnology. Available at: https://docs.wto.org/dol2fe/Pages /FE_Search/ExportFile.aspx?id=249267&filename=q/G/SPS/GEN1658R2.pdf)

* **21. Could NGTs/NGT-products raise challenges/concerns for society in general such as for the environment, human, animal and plant health, consumers, animal welfare, as well as social and economic challenges?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Certain parts of society will always be concerned about innovative products. Fortunately, a Eurobarometer indicated that levels of concern about genome editing are extremely low, and levels of concern about genetic engineering have more than halved in a decade: https://www.gmoinfo.eu/eu/articles.php?article=Most-Europeans-hardly-care-about-GMOs.
Misinformation is wide-spread in Europe on a number of topics, including on biotechnology. In some cases, public institutions fund organisations which deliberately spread misinformation.

EuropaBio strongly encourages a step change in risk communication of the EU regarding food safety: “We welcome the provisions reinforcing risk communication, and are looking forward to supporting the envisioned ‘general plan for risk communication’, provided that it ensures that risk assessors and risk managers communicate with one voice. We regret that the Commission has not proposed any actions to combat the spread and sources of misinformation that severely undermine science-based risk assessment and the credibility of EFSA.” https://www.europabio.org/agricultural-biotech/publications/eu-commission-proposal-transparency-and-sustainability-eu-risk

Next to a science-based, risk-proportionate, and product-centric future regulatory framework, open and transparent information and education of the public is required to secure buy-in and support for innovative, future-proof approaches to biotechnology that best support the ambitious EU Green Deal and Farm-to-Fork strategy.

Finally, we believe that arbitrarily giving a name (“NGTs”) to a set of technologies that merely have in common the time period when they were developed, creates irrelevant concerns in the mind of many people.

Healthcare biotechnology: It is noteworthy that viral vectors modified through NGTs for pharmaceutical applications are usually incapable of replicating in the environment, and therefore do not pose any environmental risks.

* Under which conditions do you consider this would be the case?

Misinformation is wide-spread in Europe on a number of topics, including on biotechnology. In some cases, public institutions fund organisations which deliberately spread misinformation.

EuropaBio strongly encourages a step change in risk communication of the EU regarding food safety: “We welcome the provisions reinforcing risk communication, and are looking forward to supporting the envisioned ‘general plan for risk communication’, provided that it ensures that risk assessors and risk managers communicate with one voice. We regret that the Commission has not proposed any actions to combat the spread and sources of misinformation that severely undermine science-based risk assessment and the credibility of EFSA.” https://www.europabio.org/agricultural-biotech/publications/eu-commission-proposal-transparency-and-sustainability-eu-risk

* Are these challenges/concerns specific to NGTs/products obtained by NGTs?

- ○ Yes
- ◉ No

* Please explain why not

Most concerns we are aware of do not appear to differentiate between transgenic and non transgenic organisms, and moreover, many concerns appear to be really about the economic system, rather than any particular technology per se.

* **22. Do you see particular challenges for SMEs/small scale operators to access markets with their NGTs /NGT-products?**

- ◉ Yes
- ○ No

* Please explain and provide concrete examples and data

The single most-important challenge for SMEs is the regulatory framework to which NGT products will be subjected. Disproportionate regulatory burden will stifle innovation, and will particularly affect SMEs, as they often serve more local/regional markets and cannot escape to other geographies to leverage the benefits of innovative products obtained by genome editing (at least less so than large, international corporations).

Healthcare Biotechnology: In medicine, while SMEs are well represented in the ATMP development sector, they have difficulty navigating the required additional approval for the environmental and biosafety aspects of the use and release of the GMO as they have to go to the Member States’ GMO competent authorities which often operate independently of the health authorities. There are highly fragmented procedures across the EU in terms of the classification, requirements and timings for GMO applications and approvals. SMEs lack the human and financial resources to manage this overly complex process. In addition, the several rounds of reviews result in delays which very often come at the price of ensuring the viability of small biopharmaceutical business which usually remain non-profitable for many years.

Plant Biotechnology: NGTs are efficient tools, although they do of course require significant expertise to use. As such, many SMEs have been working with NGTs. The evidence from North and South America shows that most NGT products which the authorities were consulted on were not developed by multinational companies, but by medium sized companies and public institutions. However, the EU’s GMO legislation that is currently applied to NGT products prevents SMEs from accessing the European market, at least for NGT-

derived plants. Please, refer also to several other replies where we detail the immense costs and delays of the EU's GMO import authorization system, as well as the dysfunctionality of the EU's GMO authorization system for cultivation.

*** 23. Do you see challenges/concerns from patenting or accessing patented NGTs/NGT-products?**

- Yes
- No

* Please explain why not

See our reply to question 19

The biggest concern with regard to patenting NGT innovation are potential restrictions with regard to the patentability of processes and products in the area of plant breeding and agricultural biotechnology, by introduction of Rule 28(2) EPC exclusion and the requirement of mandatory disclaimers in the examination guidelines of the EPO. It is crucial that plant products are patentable, irrespective of the way they are produced, as long as they comply with the patentability criteria of novelty, inventive step, industrial applicability, and sufficiency of disclosure and provided they are described and claimed in a clear way. Otherwise there will be a lack of legal certainty for both patentees and potential licensees.

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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E - Safety of NGTs/NGT-products

*** 24. What is your view on the safety of NGTs/NGT-products? Please substantiate your reply**

In healthcare biotechnology, the European Medicines Agency and its world-class competency to assess the safety of novel NGT-medicines is fully trusted with the thorough assessment of the safety and benefit-risk analysis before ATMPs are authorized.

For the rest, it should be emphasized that most of the purported safety risks painted in the early years of GM introduction could not be substantiated by the assessment of GM products conducted across the world. The Court of Justice's statement in Case C-528/16 that 'the risks linked to the use of those new techniques/ methods might prove to be similar to those which result from the production and release of a GMO through transgenesis' (par. 48 of the ruling) goes against the conclusions on GMO safety of numerous scientific and regulatory bodies (please see details below).

EFSA in its published scientific opinions evaluates GM crops to be as safe and nutritious as their conventional counterparts, reflecting the scientific consensus and consistent with decisions by regulatory agencies all over the world for more than 25 years. There is no evidence that a crop is dangerous to eat just because it is GM. That's the clear answer also of the Royal Society (British academy of science; https://bit.ly /3bw4IhT). Furthermore, trillions of GM meals have been eaten with zero cases of harm.

Two aspects cannot be emphasized enough in the discussion on the safety of products obtained with genome editing: (a) the intrinsic higher precision and accuracy of state-of-the-art genome editing approaches

to achieve a desired improvement of a strain as compared to the more traditional approaches; and (b) the availability and ease of DNA sequencing to confirm that the strain improvements have occured as planned.

The use of the latest genome editing techniques with their ability to produce very precise and efficient changes at targeted sites of the genomeenables better control of the product's characteristics which is an important factor to consider in safety deliberation as stated by the European Commission's Scientific Advisory Mechanism (SAM) in 2017, the 2019 statement by the Group of Chief Scientific Advisors, by the European Academies' Science Advisory Council. (https://bit.ly/2WX19vH)

The National Academy of Sciences Leopoldina, the Union of the German Academies of Sciences and Humanities, and the German Research Foundation (DFG) similarly concluded "there is currently no scientific evidence to associate directed genome editing methods with specific, novel risks. Rather, there is scientific consensus that particularly SDN-1 and SDN-2 genome edited plants are equivalent to products of traditional breeding (…)" (https://bit.ly/2Tofwsf). The topic is also covered by an easily accessible text 'Crispr hits the mark: "Paradoxically, following the court ruling, the EU subjects techniques which allow greater precision and control to a higher level of regulatory oversight (…). " (https://bit.ly/2T7zSWa)

In a recent draft opinion, EFSA's GMO Panel also could not identify any additional hazard associated to the use of the SDN-1, SDN-2 and ODM approaches as compared to both SDN-3 and conventional breeding techniques, including conventional mutagenesis. (https://bit.ly/3czhugF)

It should be pointed out that random mutagenesis through radiation or chemicals has been used for over half a century and has proven to be safely applied and controlled in the usual selection process in plant breeding. This technique has rightly not been subject to any mandatory safety assessments anywhere in the world, and it has not compromised safety. On the other hand, conventional genetic modification which produces transgenic organisms, incorporating genetic material from other species, has been practiced very widely for about three decades. It is very strictly regulated, with mandatory risk assessments, yet no actual safety issues have ever arisen from GMOs placed on the market.
Decades of experience without any safety issues arising from innovative plant breeding techniques including GMOs should lead to a more science-based, proportional approach to the regulatory oversight of plant breeding products, with a stronger focus on the product properties, rather than on the techniques used to develop the products.

We further wish to note that horizontal gene transfer across species and kingdoms is a documented natural phenomenon occurring in bacteria, fungi, animals, and plants. A recent study shows that 1 in 20 flowering plants, including many widely cultivated crops like banana, hops, cranberries, date-plums, guava, peanuts, pomelo, Suriname cherry, tea, walnuts, sweet potato, and yams, carry bacterial genes from Agrobacterium, making them 'naturally transgenic' (Matveeva and Otten, 2019: https://bit.ly/2WBk5kW, and summary by Alliance for Science: https://bit.ly/2T5NKQM).

*** 25. Do you have specific safety considerations on NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please explain

See reply to previous question

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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F - Ethical aspects of NGTs/NGT-products

*** 26. What is your view on ethical aspects related to NGTs/NGT-products? Please substantiate your reply**

Healthcare biotechnology:
In medicine, genome editing offers the prospect of saving lives and tackling some of the most devastating genetic diseases. Clinical research with genome editing of human non-heritable (somatic) cells is currently seeking to develop treatments for HIV, leukaemia, haemophilia, Leber's congenital amaurosis 10, mucopolysaccharidosis, sickle cell disease and cystic fibrosis, amongst others. Consistent with the principle of responsible stewardship of science, EuropaBio takes the position that it would be irresponsible at this time for anyone to proceed with clinical research for therapeutic use of genome editing of human germline (heritable) cells and embryos until (i) the consequences of such genome editing are more thoroughly studied and understood and (ii) a consensus on responsible and responsive global governance framework is reached. As it remains critically important that the current state of knowledge of genome editing is improved, such stay of clinical research with human germline genome editing should be limited in time and revised on a regular basis, along with the advancement of understanding of the scientific and technical environment, as well as the consensus on governance arrangements across the globe. EuropaBio takes the view that once an established governance framework will allow clinical research in genome editing of human germline cells and embryos, such research should be carried out only with the intention to potentially provide therapies to serious and unmet patient needs. EuropaBio does not support the conduct of research in germline genome editing aimed at achieving human enhancement. For detail, see the EuropaBio position paper on germline genome editing: Att. 9 & https://bit.ly/3dOWLWx

Industrial biotechnology: The ethical aspects of innovation in biotechnology should not be viewed in the light of the technologies used – but rather by looking at the product/organism and its intended uses. A number of challenges are presently facing our planet and societies: global warming, scarcity of resources, pollution, etc. Considering all of these it could be considered unethical that the European Union does not do its utmost to promote technologies and products that address some of these challenges. Industrial biotechnology (and therefore NGTs) is among such technologies, and it would just be ethical that the EU commits to using it by promoting adequate policies and legislation.

The reply for plant biotechnology follows in the next reply (to the very similar question 27)

*** 27. Do you have specific ethical considerations on NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please explain

This is a continuation of our reply to the very similar question 26 (see reply to Q 26 for healthcare and industrial biotechnology)

Plant Biotechnology: As indicated by several institutions including FAO, the increasing world population demands an increase of agricultural production by 50% until the middle of the century. Given the fact that

food scarcity and quality is one of the most critical factors for the global sustainability agenda it is also an ethical imperative to foster innovative technologies to cope with this future challenge. The nature of potential ethical concerns are in no way different than those discussed in the context of traditional genetic engineering (classical “GMOs”). For some, genome editing may be seen as interfering with mother nature, and with their religious beliefs. On the other hand, it needs to be emphasized that human beings have been interfering with natural evolution for more than 10,000 years, by selecting traits in plants and animals that are of specific and particular benefit to human beings. Since desired improvements can be achieved with higher precision and often with more subtle changes to the genetic make-up of an organism, it might potentially be argued that genome editing, particularly if restricted to an organism’s own genome sequence (i.e., without introduction of heterologous genes) might be ethically slightly more acceptable for some parts of society than traditional genetic engineering approaches.It should be stressed, though, that NOT leveraging the benefits offered by biotechnology (both traditional genetic engineering and state-of-the-art genome editing approaches) is probably more objectionable from an ethical perspective than using them (see for example Danish Ethics Council - link below). Golden Rice, as the most evident example, would have saved many lives already, if science-based, rational thinking rather than ideology had dictated regulatory and political decision making. To provide sufficient, healthy, affordable food to 10 billion people globally WILL require innovative solutions, combining “the best of all worlds”, including biotechnology. It is an ethical imperative to create the adequate regulatory and political framework to best serve society globally – and we are convinced that biotechnology, including genome editing, MUST be part of the toolbox to realize such sustainable solutions.

The prominent EU scientific bodies, including the Group of Chief Scientific Advisors of the European Commission, and the European Academies’ Science Advisory Council, the National Academy of Sciences Leopoldina, the Union of the German Academies of Sciences and Humanities, the German Research Foundation (DFG), and the Danish Council of Ethics warn of the societal cost of not using genome editing techniques and call for a reform of the GMO legal framework urging EU legislators to adopt a new science-based legal framework with proportionate requirements for the new gene-editing techniques.

(https://op.europa.eu/en/publication-detail/-/publication/a9100d3c-4930-11e9-a8ed-01aa75ed71a1
/language-en/format-PDF/source-94584603
https://easac.eu/fileadmin/PDF_s/reports_statements/Genome_Editing/EASAC_Genome-Edited_Plants_Web.pdf
https://www.leopoldina.org/uploads/tx_leopublication
/2019_Stellungnahme_Genomeditierte_Pflanzen_short_en_web_02.pdf
https://www.etiskraad.dk/~/media/Etisk-Raad/en/Publications
/DCE_Statement_on_GMO_and_ethics_in_a_new_era_2019.pdf?la=da)

EuropaBio emphasises that organisms developed with NGTs must not be subject to overregulation and disproportionate requirements, when the very same products could also be obtained through earlier breeding or classical mutagenesis methods or could simply result from spontaneous processes in nature. Only a proportionate, predictable, fit-for-purpose and science-based policy approach, providing equal regulatory treatment to equivalent products independent of their production method, will enable to leverage the full potential of genome editing to benefit citizens, the economy and the environment.

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/10_Q_26_EuropaBio_posiiton_paper_on_germline_genome_editing.pdf

G - Consumers' right for information/freedom of choice

*** 28. What is your view on the labelling of NGT-products? Please substantiate your reply**

In healthcare biotechnology, specifically, labelling requirements on novel therapies based on NGT-products should follow the same rules as for any other medicines, with no additional or different specific requirements.

For the rest, EuropaBio supports freedom of choice among safe alternatives. Mandatory labelling of NGT-derived products appears unnecessary, inappropriate and even counter-productive to achieve this goal, for several reasons.

- If NGT-derived products are captured under GM legislation, there seems to be no need nor benefit to further specify by a label what techniques have been used for product develoment
- Like products should be treated alike: Breeding techniques are not currently disclosed on labels of food products. Doing so for NGT-products would apply different standards to different techniques, even if they result in the same indistinguishable products. Treating like products differently is generally considered discriminatory under EU and international law. It would be unpracticable, create additional workload for applicants and the labelling of NGT-products would represent a new non-tariff barrier to such indistinguishable products as they do not need to be labelled in other parts of the world.
- A decision to label a consumer product should be based on criteria that are understandable and make sense for the consumers. Considering the inflation of labels and their resulting devaluation, a priority should be given to the labelling of health-related information (allergens, calories etc). Increasing transparency is a continuing, reasonable and justifiable trend. It is laudable if final customers/consumers are interested in how things are made, and what impact this has (in terms of benefits and potential risks) on the environment, nutritional quality, and health. Thus, we support to make meaningful information on production methods available to customers (e.g., through a QR code). However, labelling requirements should be restricted to what is truly meaningful in terms of food quality, food safety, and food sustainability. Again, food labels should contain science-based, meaningful information for the target use of a product, and should not contain elements that are ideologically motivated.
- Where labelling is used mainly to add marketing value voluntary labelling schemes appear more appropriate. Not least because according to Eurobarometer (June 2019), only a very small minority of EU citizens are concerned about genome editing: https://gmoinfo.eu/uk/files/510-briefing-eurobarometer-19june-2019-.pdf. Freedom of choice linked to consumer preferences that are not related to health risks should be addressed by voluntary labels and guided by market demand (unless the products in question are not authorized in the first place). For example, GMO free labelling schemes are voluntary, as are organic labelling schemes. Already today, certain organic schemes exclude certain breeding techniques from the product ranges they offer. We see no reason why they should not be able to apply similar policies to any or all NGTs, if they so desire, and as long as the information they provide is not misleading to the customers.

att; 8: EuropaBio position paper on the principles of “GM free” labelling, also oline: https://bit.ly/2z1L3Jf

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c054adac-41b2-4227-ae7c-a374c8e207f1/11_Q_28_GM_free_labelling_principles_paper.pdf

H - Final question

*** 29. Do you have other comments you would like to make?**

- (●) Yes
- ( ) No

Please provide your comments here

Some of these questions imply that it is uncertain whether products of genome editing will provide benefits, and some stakeholders appear to believe that NGT-derived products will be very similar to transgenic GMOs in terms of developers and traits. Such starting points seems inappropriate and outdated, and we hope that our substantiated replies to this questionnaire, as well as our list of products and projects, help to base the discussion on evidence rather than on unsubstantiated concerns. Genome editing is a reality and is here to stay, and its many applications are obvious from our list. The only question is whether we – as a society – are willing to provide it with a (regulatory) framework that is supporting innovation to address the pressing environmental and societal challenges that this planet currently is facing.

As additional information, on February 19, 2020, EuropaBio and the Alliance for Regenerative Medicines (ARM) organised a debate on the potential of advanced therapies for currently incurable diseases. The event, co-hosted by MEPs Claudia Gamon (Renew Europe) and Tomislav Sokol (EPP) with the following conclusions, among others:

Advanced therapies offer new therapeutic options including for currently untreatable diseases and, hence, hold great potential to improve the lives of patients and their families. There are over 7000 rare diseases and advanced therapies will first be developed in rare diseases, opening the possibility to treat more common diseases in the future.

Many patients are already benefitting from advanced therapies, and in some cases the clinical results are transformative. One-time administration can offer the potential for a permanent correction of a disease.

2019 was another year of significant growth in the development of advanced therapies. We enter 2020 prepared for continued expansion. EMA are expecting to receive up to 20 new applications for advanced therapies until the end of 2021.

The EU has a robust, science-based regulatory framework for the approval of advanced therapies which protects the safety of patients.

Europe has been leading the field in developing advanced therapies, with 14 products being granted marketing authorisation by the EMA compared to 9 by the US FDA. Europe's competitiveness needs to be maintained considering the rapid developments in North America and Asia.

The European Commission and EMA will continue listening to stakeholders and are committed to support the development of advanced therapies.

A dynamic and less fragmented regulatory environment recognising the specificities of the different technologies in their assessment process and the right incentives for continued innovation are essential for boosting the development of advanced therapies in the EU.

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Genome-Edited Products and Projects: Resources and Examples

Status 12 May 2020

This is a non-exhaustive list of over 200 genome-editing or viral vector related products and research projects, drawn from various resources and covering healthcare, industrial and agricultural biotech. Some of the sources include products from techniques other than genome editing. It is noteworthy that viral vectors modified through new genomic techniques for pharmaceutical applications are usually incapable of replicating in the environment, and therefore do not pose any environmental risks.

Contents

1. Sources with examples of various applications

1.1 US regulator's database 'Am I regulated'?

43 "NGT" applications, mostly plants, some micro-organisms

https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/Regulated_Article_Letters_of_Inquiry

As of 6 May 2020, a total of 93 Letters of Inquiry have been published by USDA replying to product developers inquiring whether their biotech applications are regulated as "GMOs" under USDA's current regulations. In the vast majority of cases, the reply by APHIS was 'No'. Please note: the majority of these letters (50 of 93) **do not involve** organisms developed using New Genomic techniques (e.g., genome editing, cisgenesis, intragenesis). Those products not developed using NGTs are excluded from analysis here. Some of these letters date back to 2011. It is not clear how many of these **43 NGT-derived organisms** that USDA has provided an opinion on are close to commercialisation. Some of them are likely not intended for commercialisation.

- **Many species**: All are plants and one mushroom. Just 34% concern one four large area crops (maize, soya, wheat, rice). The biggest group are cresses, fruit & vegetables.

- **Mainly medium companies & public research**: Only 12% of the developers are multinationals.
- **Many and varied traits:** including product quality, stress or disease tolerance. Herbicide tolerance is the rarest.

(See annex for more detailed breakdown)

1.2 EuropaBio's What if examples

https://www.europabio.org/cross-sector/publications/genome-editing-%E2%80%94-what-if-we-embraced-its-potential

11 applications: 4 healthcare, 3 plant, 3 industrial biotech & 1 animal factsheet (listed individually under the relevant sections below)

1.3 Innovature Website

https://innovature.com/

BIO and ASTA website, organised into 3 sections exploring the potential of gene-editing for our planet, our health, and our food, with about 15 concrete examples and many more conceptual examples (e.g. many examples of organisms, both plants and animals, whose genomes have been sequenced paving the way for identification of interesting genes. This could one day lead to interesting projects in these organisms.)

1.4 Gene editing regulation tracker hosted by Genetic Literacy Project

https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/

This tracker informs and compares regulatory approaches in different countries/regions for human health (distinguishing between therapeutic/stem cell and germline/embryonic), gene drives, and agriculture (distinguishing between crops/food and animals).

2. Industrial Biotech

- 3 EuropaBio industrial biotech factsheets (algae to make biofuel, enzymes to produce hydrogen peroxide without petroleum, wood into food preservatives)
- Shaping CRISPR scissors for gene editing in yeast. Research Project Wageningen
- 2 examples from Innovature (jet fuel from gene-edited pennycress, soil fertilizing microbes)
- Olefine, EU-funded research project to develop safely produced and affordable insect pheromones as an alternative to conventional insecticides
- iFermenter, EU-funded research project aiming to use biotechnology to convert forestry residual sugar streams to antimicrobial proteins by intelligent fermentation
- Genome editing for microbial protein : Microbial protein has the potential to become a sustainable, healthy, and nutritious alternative to meat and plant proteins. Genetic modification can be used to tailor the amino acid and taste profiles to serve the demands of different food applications or to eliminate potential antibiotic resistance genes.

3. Healthcare biotech

- 4 EuropaBio healthcare factsheets (targeted cancer treatments, Childhood blindness, sick blood cells, AIDS)
- Characterization of virulence genes in Streptococcus, Research Project Wageningen
- Adaptive Immunity in Prokaryotes, Research Project Wageningen

3.1 14 examples in the Gene editing regulation tracker hosted by Genetic Literacy Project:

- Liver disease - a stem cell treatment for severe liver disease was introduced in 2019 with a clinical trial to be conducted across eight European countries.
- Cancer vaccine - in 2019, researchers in Germany tested an RNA-based vaccine for patients with melanoma.
- Wiskott-Aldrich syndrome - in 2019, researchers from France and England successfully treated a rare genetic disease that causes bleeding, severe and recurrent infections, severe eczema and in some patients autoimmune reactions and the development of cancer.
- Blood disorder - gene therapy to treat beta thalassemia that reduces a patient's ability to produce hemoglobin, the protein in red blood cells that contains iron, leading to life-threatening anemia. Approved in 2019.
- Fatal muscle disease - clinical trials ongoing for gene therapy for a muscle disease in which patients typically survive only into early childhood.
- Rare form of blindness - congenital (present at birth) blindness usually caused by inherited eye diseases,
- Lymphoma - gene therapy to treat large B cell lymphoma, approved in 2018.
- Crohn's disease symptoms - A cell therapy used to treat specific severe symptoms of Crohn's disease, approved in 2018.
- Leukemia - gene therapy for patients with B cell lymphoblastic leukemia, approved in 2018.
- Vein disease - gene therapy to treat a disorder in which the small veins of the liver become obstructed, in patients who have received a bone marrow transplant, Approved in 2017.
- "Bubble boy" disease – treatment for ADA Severe Combined Immune Deficiency, a disease in children that causes them to be extremely susceptible to infections, approved in 2016.
- Eye damage – the first stem cell therapy was approved in Europe in 2015 to treat physical or chemical burns to the eye.
- Melanoma - a genetically engineered virus used to treat inoperable melanoma, conditionally approved in Europe in 2015.
- Inability to digest fats - approved in Europe in 2012 to treat lipoprotein lipase deficiency, a rare disease that leaves individuals unable to digest fats and can cause life-threatening pancreatitis.

- EU funded research: DG RTD regularly publishes success stories from EU-funded projects in biotech, specifically in health.

3.2 Other examples:

Research is currently underway on clinical applications of genome editing technologies to treat the following genetic disorders:

- Amyloidosis (abnormal proteins build up in organs, such as the heart, kidneys, liver, and can lead to their failure). and
- Clinical trials for sickle cell disease (red blood cells taking a crescent shape causing anaemia and jaundice) are ongoing.
- Haemophilia (inherited bleeding disorder where the blood does not clot properly) treatments are currently under development.
- Lysosomal storage disorders (abnormal build-up of toxic materials in cells as a result of enzyme deficiencies affecting e.g. the skeleton, brain, skin, heart, and central nervous system).
- Progress is being made on gene therapies for cystic fibrosis (the production of thick and sticky mucus, sweat or digestive juices which damages the lungs, digestive system and other organs).
- In addition, significant progress in therapeutic genome editing has been demonstrated in cancer and infectious diseases, such as HIV and Hepatitis.

3.3 EU-funded projects on CRISPR applications in healthcare, retrieved in mid-2019

The EU appears to have invested close to 200 million EUR in these projects as of mid-2019 in the 148 projects below.

Nr.	EU-funded project name	EU investment (€)	Nr.	EU-funded project name	EU investment (€)
1	Uncovering viral sabotage of host CRISPR-Cas immune systems	177.598	**75**	TRACT	2.877.077
2	Identification and Characterization of Host and Phage Proteins Interacting with the CRISPR System	100.000	**76**	CleverGenes	2.437.500
3	Prokaryotic Evolution of CRISPR Targeting	221.606	**77**	INTEGHER	1.810.747
4	PHAGECOM	183.454	**78**	ENHANCEME	161.969
5	Prokaryotic Evolution of CRISPR Targeting	221.606	**79**	OPTOLOCO	183.470
6	CRISPR-EVOL	2.495.625	**80**	LincRNA	183.470
7	CRISPAIR	1.499.763	**81**	NACHO	185.857
8	EcCRISPR	1.499.000	**82**	ACMO	2.439.996
9	REMEMBER	1.499.184	**83**	relieve-IMDs	1.500.000
10	THALAMOSS	5.020.000	**84**	editCRC	2.499.405
11	CRISPR-GQ	88.799	**85**	DUNHARROW	375.806
12	EARN	100.000	**86**	TransposonsReprogram	1.499.055
13	COHESIN CONTROL	2.421.212	**87**	FIGHT-CANCER	1.998.000
14	DIAMONDCOR	1.490.529	**88**	METLINK	173.857
15	MASTFAST	148.914	**89**	VIAR	171.461
16	IMGENE	2.068.409	**90**	Sialoglycan Array	200.195
17	SUPERSIST	5.999.997	**91**	UB-RASDisease	1.999.796
18	SYSNORM	354.112	**92**	MemCHAPS	177.599
19	EURATRANS	10.500.000	**93**	DNAProteinCrossRep	212.195
20	CVGENES-AT-TARGET	5.995.449	**94**	PathAutoBIO	200.195
21	PhageResist	2.000.000	**95**	NEMoCuRe	195.455
22	CRISS	1.372.839	**96**	UNNAMEd-2	200.195
23	PromoTeRapy	195.455	**97**	EScORIAL	1.980.434
24	ANTIVIRNA	1.467.180	**98**	INTERGLU	212.195
25	QuantFung	3.859.190	**99**	ImmunoFit	1.999.721
26	KILLINGTYPHI	183.455	**100**	iPS-ChOp-AF	1.988.750
27	eCHO Systems	4.044.794	**101**	NonChroRep	2.000.000
28	INsPiRE	2.495.050	**102**	Alpha-Synuclein	200.195
29	mTORmorS	187.420	**103**	ORGANOMICS	1.500.000
30	PlasmaCellControl	2.500.000	**104**	ANTIViR	1.499.794
31	DMD2CURE	185.076	**105**	deFIBER	1.498.544
32	UNEXPECTED	2.000.000	**106**	MALEPREG	1.499.989
33	transLEISHion	195.455	**107**	SC-EpiCode	1.500.000
34	Xchromosome	1.912.369	**108**	ELONGAN	1.480.880
35	CRISTONE	265.840	**109**	CELLNAIVETY	2.000.000
36	REACT	185.076	**110**	PD UpReg	1.999.987
37	BCSC-ST	195.455	**111**	TelMetab	2.118.431

38	PRION2020	2.500.000	**112**	MechAGE	2.500.000
39	LincRNA	183.470	**113**	Secret Surface	2.000.000
40	PLASMOESCAPE	1.815.480	**114**	SystGeneEdit	2.499.995
41	REGAIN	1.471.840	**115**	ContraNPM1AML	1.883.750
42	CHROMATINPRINCIPLES	2.495.080	**116**	GenEdiDS	2.000.000
43	EvISC	200.195	**117**	IAV-m6A	264.668
44	Cytokineproteomics	159.461	**118**	INTUMORX	1.972.905
45	HOST-SELECT	159.461	**119**	CORFEDITING	149.995
46	HemTree2.0	2.000.000	**120**	CHI-ZEF	158.122
47	3D_Tryps	1.498.175	**121**	EXO-EYE	269.858
48	HepatoRiSK	212.195	**122**	LIGER	154.721
49	MiniBRAIN	166.157	**123**	GSTHgNDD	183.455
50	SmallDrugRheuma	170.122	**124**	COLGENES	1.498.618
51	CANCER-DC	1.500.000	**125**	RetroNets	1.993.858
52	CARiPSCTcells	165.599	**126**	SPACEVAR	1.499.883
53	HD-DittoGraph	2.040.943	**127**	3D-REPAIR	1.999.750
54	DROSADAPTATION	2.392.521	**128**	reLIVE	2.571.694
55	EDPAS	158.122	**129**	MacAGE	2.499.994
56	MELANOPARK	183.455	**130**	CAVEHEART	1.499.429
57	DecipherBILU	183.455	**131**	circRTrain	3.870.807
58	MIMIC	1.057.324	**132**	HOXA9 degradome	239.861
59	Mosimann Zebrafish	100.000	**133**	CHROMTOPOLOGY	1.500.000
60	ThDEFINE	1.980.685	**134**	EpiTarget	200.195
61	HGSOC	177.599	**135**	UNICODE	1.971.846
62	NeuroRhomboid	183.455	**136**	SYNVIA	1.999.438
63	Syncrip_2014	183.455	**137**	HairGen	195.455
64	HOPE	2.484.325	**138**	EpigenomeProgramming	1.281.205
65	BRCANCER	207.584	**139**	EpiMIRgen	187.866
66	EPICut	2.196.414	**140**	INFANTLEUKEMIA	2.000.000
67	TRANSREG	1.977.148	**141**	CFS modelling	1.499.711
68	GrowCELL	2.500.000	**142**	ReachingCompleteness	1.500.000
69	ZNEOPSIN_II	183.455	**143**	SPICE	1.996.428
70	DNAmethAML	200.195	**144**	IntestineUb	195.455
71	MiRCHOL	200.195	**145**	CureCKDHeart	1.497.888
72	MeGa	195.455	**146**	IMSTREV	171.461
73	DREMATURE	187.420	**147**	LYSOSOMICS	2.362.563
74	Repro_organoid	171.461	**148**	HRMECH	1.999.014
Total Crispr-related EU investments: **196.603.910 EUR in 148 projects**					

4. Agricultural biotech, including plants and mushrooms

4.1 Products on the market

Innovator	Product	Status	Technology	Info resources
Calyxt	Soybean Calyno™ High Oleic Soybean Oil	Closed loop cultivation USA	CRISPR	Calyxt PR; Calyxt product description, AgProfessional, The Scientist

4.2 US regulator's database 'Am I regulated?

93 plant applications, of which 43 developed using NGTs – see section 1.1 and annex

4.3 National Geographic: Why gene editing is the next food revolution

https://www.nationalgeographic.com/environment/future-of-food/food-technology-gene-editing/

9 plant applications

Virus resistant cocoa, fungus-resistant banana (virus / fungus threatens a large part of the world's cocoa - banana plantations), grapevines protected against mildew (mold), coffee beans without caffeine, higher yielding rice, enhanced flavor tomatoes, drought-tolerant maize, non-browning mushroom, gluten-free wheat.

Biotech Now expands more on these same examples.

(See annex for an overview graphic)

4.4 EuropaBio 'What If' plant factsheets

https://www.europabio.org/cross-sector/publications/genome-editing-%E2%80%94-what-if-we-embraced-its-potential

Plant applications : gluten free wheat, low acrylamide potatoes, healthier oil soya.

4.5 Julius-Kühn Institut list of plants

https://www.bmel.de/SharedDocs/Downloads/Landwirtschaft/Pflanze/GrueneGentechnik/NMT_Stand-Regulierung_Anlage4-Aktualisierung.pdf?__blob=publicationFile

This list, which is probably the biggest list of plants made with 'new molecular biological techniques', is compiled by the Julius Kühn Institut (German federal research centre for cultivated plants). The JKI list is based on the 'Am I regulated' database (see 1,1), as well as on many scientific publications and lists 102 plants. The list is structured by group of traits:

- Food and Feed quality: 29, including alfalfa, peanut, potato, camelina, maize, mushroom, rapeseed, rice, sage, soy, tomato, wheat and durum wheat. 9 market ready ('Marktreife').
- Tolerance to abiotic stress: 5, including maize, rice, soy, wheat. 1 market ready.
- Tolerance/resistance to biotic stress: 16, including grapefruit, cucumber, cacao, maize, orange, rice, tomato, wine grapes, wheat. 3 market ready.
- Agronomically relevant traits: 32, including cotton, cucumber, maize, rapeseed, rice, switchgrass, lettuce, soy, tomato, wild strawberry, wheat. 2 market ready.
- Plants for industrial use: 6, including pennycress, potato, poplar, switchgrass, tobacco, sugarcane. 2 market ready.
- Ornamental plants: 3, including morning glory, orchid, flowering tobacco. 0 market ready.
- Herbicide tolerant plants: 9, including cotton, flax, potato, cabbage, maize, cassava, rapeseed, rice, and soy. 1 market ready.

- Miscellaneous: 2, including poppyseed and soy.

Of these, 83 are developed by research institutes or universities, 14 by small enterprises, and 8 by the Big 4 (this is a total of 105 because some plants are co-developed by, for instance, a research institute and a Big 4 company).

4.6 Wageningen brochure examples

The brochure 'opportunities of new plant breeding techniques' by Wageningen University and Research lists 6 examples (p. 19 ff) : late blight (phytophthora) -resistant potato using cisgenesis, blight resistant rice, powdery mildew resistant wheat, improved oil quality in soybean, resistance to AHAS (ALS)- targeting herbicides in various crops, early flowering in trees.

4.7 Plant Genome Editing Database

http://plantcrispr.org/cgi-bin/crispr/index.cgi

8 plant species

Hosted by Boyce Thompson Institute (Ithaca, NY). As of 6 March 2020, it features various entries on the following species: *Brachypodium distachyon* (grass), cassava, groundcherry, *Medicago truncatula* (barrel clover, a small legume), *Nicotiana benthamiana* (a relative of tobacco), rice, strawberry, tomato.

4.8 CropLife International

https://croplife.org/resources/

CropLife has a **case study series on Innovations in Plant Breeding** exploring the gene editing work being done to improve cassava (eliminating toxins), oranges (disease resistance), wheat (low gluten), lettuce (heat resistance), rice (rice blast resistance), and beans (drought tolerance, nutrition, storage).

4.9 CRISPR Advent Calendar from Progressive Agrarwende

https://progressive-agrarwende.org/crispr-adventskalender-blog/

In December 2019 Progressive Agrarwende released a CRISPR advent calendar with 24 case studies covering a variety of traits:

- Disease resistance (7 case studies: barley, cassava, potato, rapeseed, banana, orange, wine)
- Agronomic traits e.g. drought tolerance, seed dormancy, growth characteristics (10 case studies: Wheat, Watermelon*, Cucumber, Cotton, Maize, Rapeseed, Kiwifruit, Wild tomato, and 2 traits in rice (salt tolerance and reduced arsenic content)) *herbicide resistance
- Consumer benefits e.g. increased vitamins, improved oil quality or benefits to a processor e.g. starch composition, increased biomass (5 case studies: Dandelion, Lettuce, Tomato, Potato, Soybean)
- Ornamentals e.g. enhanced flower longevity or modified colours (2 case studies: petunia, wishbone flower)

4.10 Innovature

Innovature cites examples like compactly-growing cherry tomatoes, acceleration of domestication of the wild tomato, disease resistant apple, banana, cacao, pumpkin, sweet potato, reduced-browning potatoes.

4.11 Genetic Literacy Project Gene editing regulation tracker

https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/

The Gene editing regulation tracker hosted by Genetic Literacy Project cites 87 products and research projects, only 4 of which are linked to herbicide resistance (canola, soybean, maize). These are broadly distributed worldwide:

- North America (USA, Canada): 25 projects, including apple, canola, potato, alfalfa, soybean, tomato, wine grapes, rice, wheat, camelina, mushroom. These examples cover disease/pest resistance (tomato, wine grapes, wheat, rice), abiotic stress tolerance (rice, soybean, maize), agronomic benefits (cereal crops, alfalfa), consumer benefits (soybean, tomato, apple, wheat, camelina, potato, mushroom)
- Central and South America (Brazil, Colombia, Chile, Uruguay, Argentina): 17 projects, including rice, cassava, cacao, soybean, mandarin, tomato, potato, alfalfa, camelina, maize, yeast. These examples cover disease/pest resistance (soybean, rice, cassava), abiotic stress tolerance (maize, rice, alfalfa), consumer benefits (tomato, maize, mandarin, soybean, camelina, cacao, potato, cassava), biofuel production (yeast).
- Africa: 10 projects, including cassava, bananas, yam, maize, sorghum, cacao. These projects focus on disease or pest resistance (cassava, bananas, yam, maize, sorghum, cacao), abiotic stress tolerance (banana) or on nutritional qualities (cassava, sorghum).
- Europe, Russia, Israel: 16 projects, including tomato, petunias, jasmine tobacco, cucumber, maize, banana, canola, wheat, potato, camelina, barley, beetroot, sugar beet. These mainly cover disease resistance (banana, cucumber, tomato, potato, sugar beet), abiotic stress tolerance (maize, barley) or consumer benefits (wheat, potato, camelina, beetroot, petunia, jasmine tobacco).
- Asia (concentrated in China, India and Japan): 21 projects, including rice, banana, maize, wheat, grape, kiwifruit, poplar, soybean, morning glory, apple, tomato, potato, canola. The examples cover disease/pest resistance (wheat), consumer benefits (rice, morning glory, tomato, potato, banana), agronomic benefits (rice, wheat, soybean), research (grape, kiwi, poplar, apple, tomato).
- Australia and NZ: 10 projects, including sorghum, wheat, barley, cottonseed, canola, potato, rice, grass. These examples cover disease/pest resistance (barley, wheat), agronomic traits (wheat, canola, grass), consumer benefits (cottonseed, potato, rice, sorghum).

4.12 Resources about specific plant applications

- ALFALFA: improved digestibility (2021): Calyxt pipeline website
- BANANA: fungus resistance (against the devastating Panama disease): Wageningen & Queensland.
- BERRIES: including raspberries and blackberries, to extend growing season, improve nutrition – Pairwise in partnership with Plant Sciences Inc
- CABBAGE: earlier flowering (Chungnam and Seoul National Universities), male sterility (Southwest University, China)
- CASSAVA: resistance to cassava brown streak disease (Donald Danforth Plant Science Center) and lower toxin production (by Innovative Genomics Institute – collaboration between UC Davis and UC Berkeley)
- CITRUS fruits, incl. ORANGE: resistance to citrus greening Innovature, CLI & ASTA video
- COCOA: fungus resistance – Pennsylvania State
- COFFEE: disease & pest resistance. Research project UC Davis (via Innovature)
- DANDELION: enhanced agronomic performance (easier to cultivate & harvest taproot phenotype, higher root biomass, increased natural rubber biosynthesis) – University of Münster, Ohio State University
- GRAPE mildew resistance, saving fungicides: Articles in GLP, Innovature
- GROUNDCHERRY research project Cornell University (also here and here)

- LETTUCE Video : Climate vs. Lettuce. CLI & ASTA Video
- MAIZE: Thermosensitive male-sterile maize (Chinese Academy of Agricultural Sciences)
- MAIZE: haploid breeding lines (Chinese Academy of Agricultural Sciences)
- MAIZE: reduced epicuticular wax (Iowa State University, China Agricultural University)
- MUSHROOM non-browning (non-regulated in USA): articles in Nature, Washington Post
- OILSEED RAPE research project University of Kiel
- OILSEED RAPE resistance against sclerotinia stem rot Yangzhou University
- PLANTAIN with inactivated endogenous Banana streak virus (International Institute of Tropical Agriculture & UC Davis)
- POPLAR TREE – Thuenen Institute
- POTATO *Phytophthora* resistance and starch: Swedish University of Ag Sciences.
- POTATO: cold storable (post 2024): Calyxt pipeline website
- POTATO: Resistance to potato virus Y which also confers salt and osmotic stress tolerance (Moscow State University)
- RICE : more robust rice (attacking TAL effectors) : Research project Cornell Univ.
- RICE: haploid breeding lines (Chinese Academy of Sciences)
- SUGARCANE: improved saccharification efficiency (University of Florida and Korea Institute of Science and Technology)
- TOMATO : disease resistance. Research project Boyce Thompson Institute
- WHEAT : reducing acrylamide in processed wheat. Project Rothamsted.
- WHEAT : high fiber (2022): Calyxt pipeline website
- WHEAT : mildew resistance: Chinese Academy
- WHEAT : longer seed dormancy period (Japanese National Agriculture and Food Research Organization)
- WINE GRAPES : fungal resistance: University of Udine

4.13 23 EU-funded projects on CRISPR applications in agriculture (retrieved in mid-2019)

The EU appears to have invested close to 27 million EUR in these projects as of mid-2019.

Nr.	EU-funded project name	EU investment (€)
1	PlantMYCcellWall	265.263
2	CRISPR/Cas9 technology implementation for improved resistance to Abiotic Stress in cereals:	72.500
3	Next generation disease resistance breeding in plants	2.496.835
4	Multidimensional CRISPR/Cas mediated engineering of plant breeding	2.499.981
5	Mechanisms of natural auto immunity triggered by plant NLR immune receptors	159.460
6	Tracking and Targeting a T-DNA Vector for Precise Engineering of Plant Genomes	1.958.408
7	Implementation of CRISPR/Cas9 technology in melon to edit fruit ripening and CMV resistant genes	170.121
8	New insights into wheat meiosis: Crossover resolution in the absence of the Ph1 locus	183.454
9	Control of meiotic recombination: from Arabidopsis to crops	3.645.642
10	BIO: Banana IN and OUT - engineering resistance against Panama disease in banana	183.454
11	DISCO	6.485.847
12	BREED4FUTURE	265.263
13	Increasing reproductive success in crops under high ambient temperature	158.121
14	GENETICS OF TEMPERATURE MODULATION OF PLANT IMMUNITY	100.000
15	Molecular inventions underlying the evolution of the nitrogen-fixing root nodule symbiosis	2.494.114

16	GREEN-SPECIALISTS	200 194
17	Max-imising the potential of CROP researchers	1.467.957
18	SiPoMorph	183.454
19	SynthHotSpot	1.999.953
20	CVI_ADAPT	1.609.375
21	MEPOL	165.598
22	MetKnock	150.000
23	CHIC project (see below)	7.300.000
Total Crispr-related EU investments		**34.214.994**

4.14 Other EU projects

- Moritz Nowack - ERC consolidator grant 1/06/20-31/05/2025
  EXECUT.ER exploits CRISPR-based mutant screens and multiplex genome editing to dissect the molecular mechanisms that execute developmental programmed cell death in plants. (EXECUT.ER)
- Dirk Inzé - ERC Advanced grant 1/09/2019-31/08/2024
  A novel breeding strategy using multiplex genome editing in Maize (BREEDIT)
  BREEDIT combines multiplex genome editing with classical breeding to select for maize plants with superior growth characteristics.
- Wout Boerjan - ERC Advanced grant 1/07/2019-30/06/2024
  Large-scale identification of secondary metabolites, metabolic pathways and their genes in the tree model poplar (POPMET)
  POPMET will use gene editing as a reverse genetics tool in the discovery of metabolic pathways in poplar.
- CHIC: The CHIC project aims to develop chicory varieties that can be used to produce dietary fibre with enhanced prebiotic effects to promote gut health. At the same time, given its biosynthetic capacity, high yields and low agronomic requirements, chicory has significant potential as a versatile production host in molecular farming for the production of many additional health-related products with benefits for consumers. CHIC also aims to harness this potential for the extraction of other types of health-related compounds (terpenes) as potential lead molecules for drug development.

4.15 Other relevant plant focused resources

- Plant Ed (EU funded COST action project): https://plantgenomeediting.eu/about-planted/objectives/ (no product examples)
- Video (ASTA): Plant Breeding Innovation: https://www.youtube.com/watch?v=nYMoWtTXkwI
- TED talk from Jennifer Doudna: How CRISPR lets us edit our DNA
- KWS video: usefulness of genome editing in crops explained generally: yield, climate, disease; good legislation important; also transparency and discussion important (pictures of some crops, e.g. potatoes, maize, etc.). Also, lots of good general GE explanation (e.g. glossary on KWS website).
- Pioneer video on CRISPR-Cas
- ASTA-CLI: PBI video and CLI infographic with general benefits explained
- Good pictures links for before and after domestication (e.g. teosinte versus modern maize) here and here.
- PRRI resources; ISAAA website

5. Animals

- The FLI report (Friedrich-Loeffler-Institut : Institute reporting to the German Ministry of Agriculture) lists ca. 100 animals, mostly transgenic, both green and red (animals to produce medicines).
- EuropaBio animal factsheet (hornless cows, sterile pigs to avoid manual dehorning and pig castration)
- Pigs disease resistance. Research project Roslin Institute (Edinburgh)
- Tilapia, which allows for a 70% yield increase, Intrexon press release
- Innovature cites the following examples: Lyme-disease resistant mice, malaria-resistant or sterile mosquitoes, flu-resistant chickens
- Gene editing regulation tracker hosted by Genetic Literacy Project cites 78 products and research projects. These are broadly distributed worldwide:
  - North America (USA, Canada): 12, including Aquadvantage salmon, cows, pigs, catfish, lizards, coral
  - Central and South America (Brazil, Chile, Uruguay, Argentina): 9, including fruit flies, cows, tilapia, horses, salmon
  - Africa: 7, chicken, rhino, mostly cows
  - Europe and Israel: 12, including pigs, sheep and chickens, mice, flies
  - Asia (concentrated in China, India and Japan): 29, including pigs, monkeys, dogs, cows/heifers, goats, mosquitoes, mice, rats, coral, and fish (tuna, anchovy, red sea bream)
  - Australia and NZ: 9, including toad, carp, cattle, chickens, mice, coral

Annex 1: US regulator's database 'Am I regulated?'

https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/Regulated_Article_Letters_of_Inquiry

Status 6 May 2020

As of 6 May 2020, a total of 93 Letters of Inquiry have been published by USDA replying to product developers inquiring whether their biotech applications are regulated as "GMOs" under USDA's current regulations. In the vast majority of cases, the reply by APHIS was 'No'. The majority of these letters (50 of 93) **do not involve** organisms developed using New Genomic techniques (e.g., genome editing, cisgenesis, intragenesis). Those products not developed using NGTs are excluded from analysis here.

MAINLY MEDIUM COMPANIES AND PUBLIC RESEARCH

The signatory organisations (mostly developers) of the 43 requesting letters were:
1. 46% medium sized and smaller companies : 20 letters;
2. 42% public institutions : 18 letters ; mainly universities;
3. 12% multinational companies which also market transgenic GMO plants (BASF, Bayer, Corteva (DupontPioneer and Dow), Syngenta, Simplot) : 5 letters

Only 12 % of the developers are multinational companies

MANY DIFFERENT ORGANISMS, MOSTLY PLANTS, BUT MANY SPECIES

The letters with relevance to plants covered a very wide variety of species:
1. 16% Fruit & vegetables : 7 (tomato, grapevine, apple, citrus, lettuce)
2. 14% Maize : 6
3. 12% Forages & Cresses : 5
4. 12% Soy : 5
5. 7% Potato: 3
6. 5% Wheat : 2
7. 5% Rice : 2
8. 23% Other: 10 (flowers, Camelina, Setaria, tobacco, sorghum)
9. 5% no crop specified: 2
10. 2% Mushroom : 1

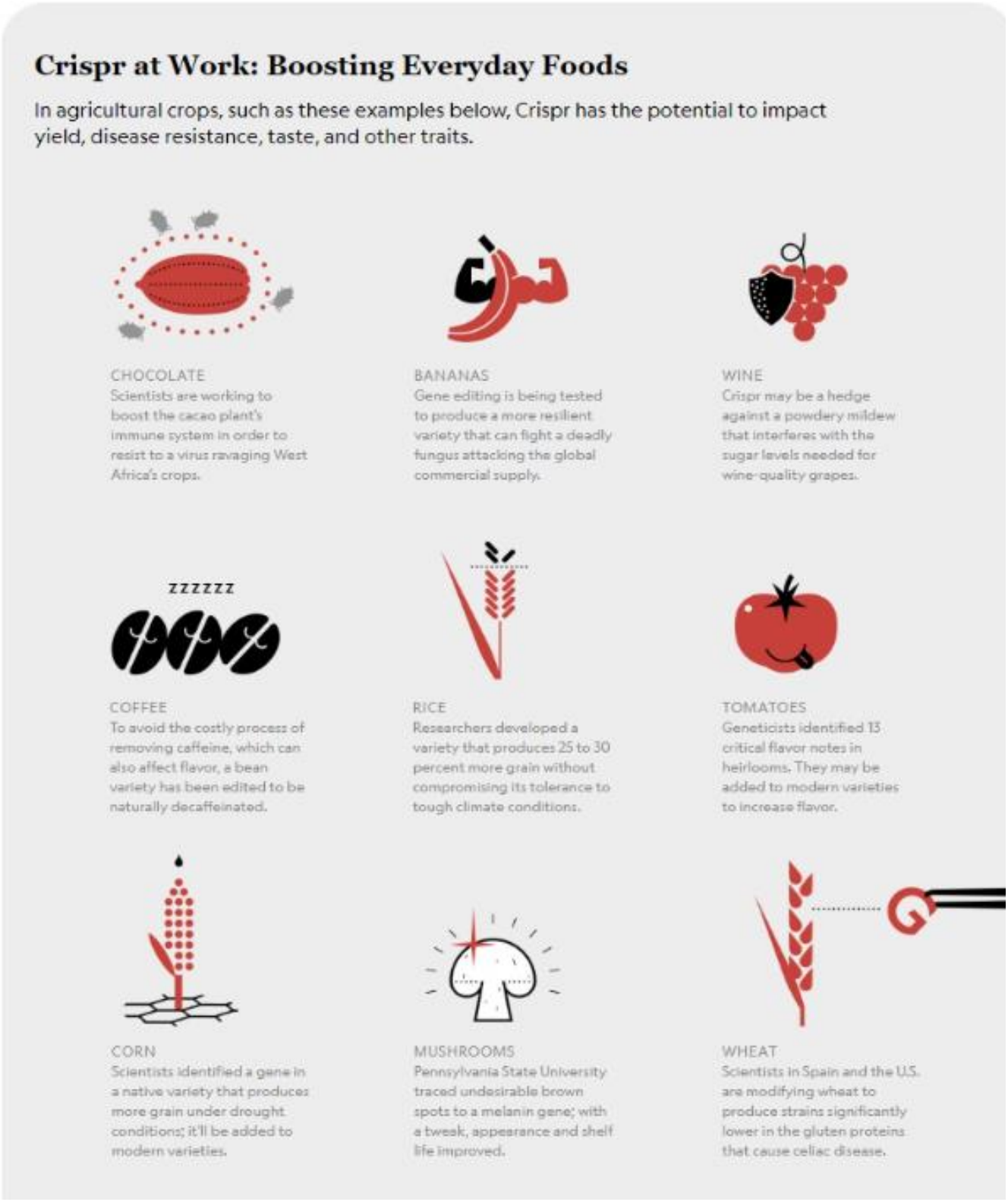
Only 26% concern the big four crops (soy, maize, oilseed rape and cotton), namely 6 maize and 5 soy

MANY DIFFERENT TRAITS

1. Product Quality: 18
2. Pest Resistance: 6
3. Agronomic Phenotype: 5
4. Stress Tolerance: 3
5. Other traits: 7
6. CBI: 3

The biggest group of traits concern product quality, disease resistance and stress tolerance, and agronomic phenotype. Herbicide resistance seems to be the rarest trait.

Annex 2: Screenshot of National Geographic reporting on 9 plant applications



Why gene editing is the next food revolution
https://www.nationalgeographic.com/environment/future-of-food/food-technology-gene-editing/
9 Plant Applications (National Geographic)

Annex 3: Screenshot of DG Research Success Stories Health & Life Sciences: Biotechnology

Advanced molecular technique boosts cancer research

After cardiovascular diseases, cancer is the second leading cause of death and morbidity in European countries and is one of the most significant health challenges worldwide. An EU-funded project is developing new tools for diagnosing cancer and for understanding the role of proteins in this and other major diseases.

Published: 14 March 2019

Light-sensitive molecules for new disease therapies

Peptidomimetics are small molecules that mimic short natural proteins - peptides - and produce the same effects as their natural counterparts. An EU-funded project is developing peptidomimetics that can alternate between biologically active and inactive forms when exposed to light. The technique could lead to new light-controlled drugs which can be turned off and on when needed to treat cancers and other diseases.

Published: 4 March 2019

Personalised brain cancer treatment shows potential

EU-funded researchers have demonstrated huge potential for treating aggressive brain cancer using actively personalised immunotherapy in a first first-stage clinical trial to test the vaccine's safety.

Published: 27 February 2019

DG RTD project website: "Success Stories Health & Life Sciences: Biotechnology"
https://ec.europa.eu/research/infocentre/theme_en.cfm?item=Health%20%26%20life%20sciences&subitem=Biotechnology

PRICING INNOVATION OUT OF THE EU

COUNTING THE COSTS OF GMO AUTHORISATIONS

EuropaBio
The European Association for Bioindustries

Each year, around **18 million farmers around the world plant genetically modified (GM) crops for higher yields, improved crop quality and the ability to use fewer inputs**. Although the vast majority of EU farmers are not allowed to grow GM crops, the EU is one of the biggest importers of agricultural commodities derived from GMOs. In fact, the GM soya beans which are imported into the EU each year weigh as much as the entire EU population!

Before coming onto the market, **all GM crops go through a rigorous and costly safety assessment**. In the EU, this assessment is carried out by the European Food Safety Authority (EFSA).

EU GMO AUTHORISATION COSTS AND TIMELINES ARE PROHIBITIVE

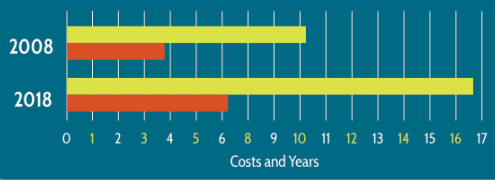
AN EU IMPORT AUTHORISATION FOR GM CROPS CURRENTLY:

Costs an estimated **€11 – €16.7 million**[1]

And takes over **6 years** to be completed on average!

... And this is just for import. The system for authorisations to cultivate in the EU is not functioning at all.

COSTS AND WAITING TIME HAVE INCREASED FOR OVER A DECADE



COMPARED TO 10 YEARS AGO, THAT'S:

- Almost **two thirds** more **expensive**
- Almost **two thirds** more **time consuming**

REGULATORY BURDEN HAS BLOWN OUT OF PROPORTION...

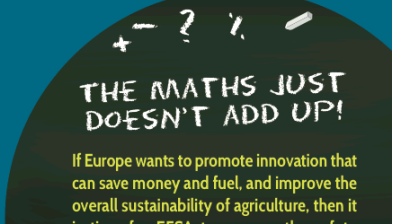
COMPARED TO OTHER REGULATED PRODUCTS THAT'S:

- More than **7 times as long** as an EU authorisation for human medicines
- **Much more expensive and lengthy** than EU authorisations for other food related products

AND COMES AT A COST

IT IS NO SURPRISE THAT...

- **EU farmers lack fair access to GM crops**
- **Only 1 EU authorisation** currently exists for cultivating a single GM crop, and this authorisation dates back to 1998
- Other authorisation files for cultivation have been **lingering in the system for 15 years** and longer despite multiple confirmations of product safety
- **Innovators have withdrawn most cultivation applications from the system**, and are now focusing their product development pipelines on other parts of the world



If Europe wants to promote innovation that can save money and fuel, and improve the overall sustainability of agriculture, then it is time for EFSA to manage the safety assessment as efficiently as other agencies do, and give farmers improved and timely access to GM crops.

EuropaBio
The European Association for Bioindustries

[1] This is an industry estimate based on a 2008 report issued by the Dutch government advisory body on GMOs: https://bit.ly/2GuQh38 (accessed 19-12-18).

7. Does your sector have experience or knowledge on traceability strategies, which could be used for tracing NGT-products?

Yes

No

Not applicable

The traceability of NGTs will be one of the biggest challenges in terms of compliance with the current GMO legislation. Companies use their stewardship and quality systems to comply with legislation and exchange information about the products they buy and sell. Traceability would be much easier to guarantee if the legislation focused on the properties of the products/ organisms more than on the technologies used to make them.

Healthcare biotechnology:

Traceability requirements as applicable for medicinal products will be followed for medicines based on NGT-products. Most notably, Regulation (EC) No 1394/2007 Article 15, requiring the submission of a risk management plan has to be submitted in accordance with the current EU legislation and pharmacovigilance guidelines. Track and trace systems for individual products which keep the collected data for 30 years are also required. In addition, the Guidance EMEA/CHMP/GTWP/60436/2007 and the Guideline on GMP for ATMPs Vol IV para IV C(2017) 7694 provide for additional recommendations on traceability. Therefore, additional traceability strategies will not be necessary since viral vectors and genetically modified human cells are incapable of replication or long-term survival in a release environment.

Industrial biotechnology:

Companies have a traceability system already in place, namely the quality system they use to secure that their products are fully compliant with applicable legislation. As part of these systems, there is regular information exchange between suppliers and their customers about the compliance of products in the relevant jurisdictions, including whether products fall under the GMO legislation of any relevant jurisdictions.

For contained use microorganisms, there is no need for traceability since they remain in the production premises. Still for fermentation products for food and feed purpose there is a requirement for residual DNA analysis that is specific for a specific genetically modified microorganism. For live microorganisms, we could think of the following strategies:

Microorganisms that have been modified in ways that are analogous to transgenesis could be subject to documentary traceability. In addition to this, there would be the possibility to perform an analytical traceability, based on the microorganism's single genetic characteristics that were described by the applicant when applying for authorization for deliberate release. The latter option would however require significant resources and technology at control laboratories.

Microorganisms that cannot be distinguished from counterparts made with traditional techniques or even natural counterparts are more challenging to track. Paper tracing may be possible to some extent for such icroorganisms. are difficult to track.

Plant Biotechnology:

EuropaBio members are not aware of an effective, enforceable traceability system that could be used for detecting NGT-products. Approaches that can be used to fulfil traceability requirements foreseen in the GM legislation (e. g. identity preservation or paper trail records, etc.) can be applied to niche and value added products but would be highly challenging to implement for commodities.

Furthermore, some genome edited plants have genetic changes that could also have been obtained through earlier breeding methods or resulted from spontaneous processes in nature. For this reason, traceability approaches used for GMOs can not always be appplied to NGTs.

As part of the GMO authorisation process, methods for detection and identification of the GMO need to be provided and consequently validated by the European Union Reference Laboratory for GM Food and Feed. GMO detection methods are based on the identification of a specific transformation event.. However, the event-specific approach cannot be applied uniformly to all NGT products, depending on the nature and extent of the edits.

In many cases, it may be impossible to distinguish if a given mutation was achieved by a particular mutagenic method or is the result of a natural process. EuropaBio concurs with the findings of the European Network of GMO Laboratories' (ENGL) report (Att 4 & https://gmo-crl.jrc.ec.europa.eu/doc/JRC116289-GE-report-ENGL.pdf) that genome edited plants cannot be detected with the current GMO screening strategies targeting common sequences used in the development of transgenic GMOs. They assert that it is questionable if event-specific identification and quantitative detection methods can be developed readily for all NGT plants. For instance, detection methods for those plant products that are characterised by a non-unique DNA alteration will probably lack the specificity required to identify the NGT plant. Moreover, accurate quantification may be challenging if only changes of just one or a few base pairs are introduced. The ENGL therefore concludes that the validation of an event-specific detection method and its implementation for market control is not feasible for NGT plant products carrying a DNA alteration that is not unique.

For the purposes of detection and identification, applicants are required to develop a unique identifier as defined by regulation EC N° 1830/2003 for each GMO. If NGT derived products are classified as GMOs, this requirement would apply even when the resulting product does not carry a novel combination of genetic material that could be obtained by recombinant DNA technology. Assigning a unique identifier to such products would contradict the regulatory and policy approaches of several countries (including Chile, Brazil and Colombia) to treat certain genome edited products as conventional breeding products, not covered by their GMO laws (i. e., no OECD unique uidentifier needed). The Inclusion of NGT products in the same OECD product database and with the same identification principles as used for GMOs would disseminate incorrect information about the genetic makeup of genome edited products and create confusion among stakeholders (global regulatory authorities, growers, grain trade, value chain, or consumers). Only if NGTs are used to generate transgenic plants, the unique identifier should be assigned in accordance with established international practices.

Detection of food and feed plant products obtained by new mutagenesis techniques

European Network of GMO Laboratories (ENGL)

Report endorsed by the ENGL Steering Committee

Publication date: 26 March 2019

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JRC116289

How to cite this report: European Network of GMO Laboratories (ENGL), *Detection of food and feed plant products obtained by new mutagenesis techniques*, 26 March 2019 (JRC116289)

Contents

Executive summary

The European Network of GMO Laboratories (ENGL) has reviewed the possibilities and challenges for the detection of food and feed plant products obtained by new directed mutagenesis techniques leading to genome editing. The focus of this report is on products of genome editing that do not contain any inserted recombinant DNA in the final plant.

The procedures for the validation of detection methods as part of the **market authorisation** application process for genome-edited plant products will in principle be the same as for the current conventional GMOs. It is, however, questionable if event-specific identification and quantitative detection methods can be developed readily for all genome-edited plants. For instance, detection methods for those plant products that are characterised by a non-unique DNA alteration will probably lack the specificity required to identify the genome-edited plant. Moreover, accurate quantification may be challenging if only changes of just one or a few basepairs are introduced.

The EU Reference Laboratory for Genetically Modified Food and Feed (EURL GMFF) assisted by the ENGL will need to review the minimum performance requirements that are applied for GMO method validations in view of the specific characteristics of genome-edited plants. This should provide further guidance to applicants for market authorisation and to the EURL GMFF for validation of the event-specific methods. For example, it is currently unclear how to demonstrate or assess the specificity of the method if the mutation could also occur spontaneously or could be introduced by random mutagenesis techniques. Furthermore, it needs to be emphasised that specific detection methods would be required to cover all DNA alterations in a multi-edited plant.

For **market control**, considering the current knowledge and state of the art of GMO testing, it is highly improbable for enforcement laboratories to be able to detect the presence of unauthorised genome-edited plant products in food or feed entering the EU market without prior information on the altered DNA sequences. The PCR (polymerase chain reaction)-based screening methods that are commonly used to detect conventional GMOs cannot be applied nor could be developed for genome-edited plant products. The reason is that the currently used screening methods are targeting common sequences which are not occurring in genome-edited plants.

DNA sequencing may be able to detect specific DNA alterations in a product. However, this does not necessarily confirm the presence of a genome-edited plant product. The same DNA alteration could have been obtained by conventional breeding or random mutagenesis techniques, which are exempted from the GMO regulations.

In conclusion, validation of an event-specific detection method and its implementation for market control will only be feasible for genome-edited plant products carrying a known DNA alteration that has been shown to be unique. Under the current circumstances, market control will fail to detect unknown genome-edited plant products.

Several issues with regard to the detection, identification and quantification of genome-edited products are currently based on theoretical considerations only and lack any experimental evidence. Therefore, they will require further consideration.

1 Introduction

In the European Union the authorisation system for the introduction of GMOs in the agro-food chain is governed by stringent legislation to ensure:

- the safety of food and feed for health and the environment;
- consumers' choice between GM, organic and conventionally-produced food;
- the functioning of the internal market, *i.e.* once authorised, GM products can be placed on the market anywhere in the EU[1].

The EU policy on GMOs is comprehensive as it addresses the development of GMOs, the stepwise release into the environment, the general cultivation and seed production, marketing, labelling, enforcement and the whole agro-food chain, up to the consumption by humans and animals.

The EU Reference Laboratory for Genetically Modified Food and Feed (EURL GMFF), hosted by the Joint Research Centre (JRC) of the European Commission, is legally mandated to assess and validate the detection methods submitted by the applicants (GMO producers) for authorisation of GMOs[2]. For this task, the EURL GMFF is assisted by a consortium of national reference and enforcement laboratories, known as the European Network of GMO Laboratories (ENGL), which has issued a guidance document explaining the minimum performance requirements (MPR) for analytical methods of GMO testing[3]. Since the labelling and traceability legislation[2,4,5] is based on the GMO content present in the food or feed product, one of the requirements refers to the accurate quantification of the 'GM fraction' in such products. GMOs or GM food and feed products that do not meet the requirements of the legislation should not be present on the market (see Text box 1).

The EURL GMFF also has a legal mandate under the 'Official Controls Regulation'[6], which defines harmonised rules on official controls and, among others, activities performed to ensure compliance to the food and feed laws related to the presence of GMOs. In that context, official enforcement should control the implementation of the labelling requirements and prevent infringement of the legislation due to the presence of unauthorised GMOs on the market. To implement this Regulation, Member States have appointed National Reference Laboratories (NRLs) and official laboratories to perform analyses on food, feed and seed products in their national markets; this is performed by applying – when available – first-line screening methods to detect commonly used genetic elements in known and unknown GMOs and, thereafter, the identification and quantification methods validated for the authorised GMOs.

[1] In line with Directive (EU) 2015/412 Member States may, however, restrict or prohibit the cultivation of an authorised GMO on all or part of their territory.

[2] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed. *Off. J. Eur. Union* L268:1-23.

[3] European Network of GMO Laboratories (2015) Definition of minimum performance requirements for methods of GMO testing (http://gmo-crl.jrc.ec.europa.eu/doc/MPR%20Report%20Application%2020_10_2015.pdf).

[4] Regulation (EC) No 1830/2003 of the European Parliament and of the Council of 22 September 2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC. *Off. J. Eur. Union* L268:24-28.

[5] Commission Regulation (EU) No 619/2011 of 24 June 2011 laying down the methods of sampling and analysis for the official control of feed as regards presence of genetically modified material for which an authorisation procedure is pending or the authorisation of which has expired. *Off. J. Eur. Union* L166: 9-15.

[6] Regulation (EU) 2017/625 of the European Parliament and of the Council of 15 March 2017 on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection products (Official Controls Regulation). *Off. J. Eur. Union* L95:1-142.

Text box 1

Different authorisation statuses of GMOs under Directive 2001/18/EC[7] and Regulation (EC) No 1829/2003[2]

Authorised for placing on the market

Authorised GM material is allowed on the EU market. Authorisation mostly concerns the import of GMOs and products thereof and their use in food and feed. Few authorisations have been submitted for cultivation of GM plants and currently only one GM maize event is authorised for cultivation.

GMOs in this category can be present on the market in food and feed material. Validated identification and quantification methods and reference materials are available for these GMOs. According to Directive 2001/18/EC, Regulation (EC) No 1829/2003 and (EC) No 1830/2003, the presence of such authorised GMOs in food and feed shall be indicated on the label of the product. Labelling requirements do not apply for GMOs intended for food, feed or direct processing when the presence is at or below 0.9% and provided that these traces are adventitious or technically unavoidable.

Non-authorised for placing on the market

- GMOs that have been authorised for any other purpose than for placing on the market, under Part B of the Directive 2001/18/EC. The authorisation for these purposes (*e.g.* experimental uses and field trials) is granted and applied at national level.
- GMOs that have **not** been authorised for placing on the market, as or in products, under Directive Part C of 2001/18/EC or Regulation (EC) No 1829/2003.
- Pending authorisation: a valid application for authorisation in the EU has been submitted under Directive 2001/18/EC or Regulation (EC) No 1829/2003.
- Authorisation expired: a GMO of which the authorisation has expired and no renewal application has been submitted.

GMOs in these categories are not allowed on the EU market and a zero-tolerance applies.

For feed use only, and under the conditions of Commission Regulation (EU) No 619/2011[5], GMOs in the latter two categories shall be considered non-compliant at or above the Minimum Required Performance Limit (MRPL) of 0.1% related to mass fraction, and findings below the MRPL shall be notified to the Commission and other Member States. For pending authorisations, the requirements are that the GM material must be authorised for commercialisation in a third country, a valid application had been submitted to the EU and has been pending for more than three months, no adverse effects have been identified by EFSA when present under the MRPL, and a validated quantification method and certified reference materials are available. For expired authorisations, certified reference materials have still to be available.

During the past years, several new plant breeding techniques, including targeted mutagenesis techniques generically called 'genome editing', have been employed to create diversity for exploitation in plant breeding (reviewed in [8]). Instead of the random mutation of many genes at the same time (as in conventional mutation breeding techniques) or the random insertion of new genes (as in conventional GMOs), genome editing allows the site-specific alteration of the DNA sequence of one or a few selected genes; this can result in single nucleotide variants (SNV) or sequence insertions or deletions (InDels). These DNA alterations may be present either in a homozygous or heterozygous state in the genome, *i.e.* all or only a fraction of the copies of a given gene (called the alleles of a gene) may carry the alteration (*e.g.* in a tetraploid (4n) plant the same DNA alteration can be present as DNA copy between one and 4 times)[9,10,11].

[7] Directive 2001/18/EC of the EuropeanParliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. *Off. J. Eur. Comm.* L 106:1-38.

[8] Scientific Advice Mechanism (2017) New techniques in Agricultural Biotechnology. European Commission (https://ec.europa.eu/research/sam/pdf/topics/explanatory_note_new_techniques_agricultural_biotechnology.pdf#view=fit&pagemode=none).

[9] Clasen, B.M., Stoddard, T.J., Luo, S., *et al.* (2016) Improving cold storage and processing traits in potato through targeted gene knockout. *Plant Biotechnol. J.* 14:169-176.

[10] Haun, W., Coffman, A., Clasen, B.M., *et al.* (2014) Improved soybean oil quality by targeted mutagenesis of the fatty acid desaturase 2 gene family. *Plant Biotechnol. J.* 12:934-940.

[11] Demorest, Z.L., Coffman, A., Baltes, N.J., *et al.* (2016) Direct stacking of sequence-specific nuclease-induced mutations to produce high oleic and low linolenic soybean oil. *BMC Plant Biol*. 16:225.

In 2011, upon request of DG SANTE, the JRC reviewed the state-of-the-art of some of the emerging new plant breeding technologies, their level of development and adoption by the breeding sector and the prospects for a future commercialisation of plants created by these techniques[12]. Additionally, with support of several ENGL experts, the challenges for the detection of organisms developed through these techniques were evaluated[13]. The topic has since been discussed also during meetings of the ENGL. In the past few years, a novel innovative technique for genome editing, CRISPR-Cas, with wider potential and easier applicability, has rapidly advanced plant biology research and the development of applications for plant breeding[8,14].

In 2018, the European Court of Justice ruled that organisms obtained by new mutagenesis techniques, *i.e.* genome editing, in contrast to conventional mutagenesis techniques *"that have conventionally been used in a number of applications and have a long safety record"*[15], are not exempted from the GMO legislation[15]. In October 2018, the JRC received a mandate from DG SANTE to elaborate, together with the ENGL, on the implications of this ruling for the detection of such organisms.

This document addresses questions related to the new analytical challenges for the detection, identification and quantification of genome-edited food and feed products of plant origin. Those may relate (1) to the compliance with the GM food and feed legislation, including the requirements for method validation as part of the GMO authorisation procedures[2], and (2) to the provisions of the Official Controls Regulation[6] on the routine testing of food and feed by the enforcement laboratories.

This document has been endorsed and released for publication by the Steering Committee of the ENGL.

The ENGL experts who mentioned their viewpoints here have an in-depth expertise with respect to GMO analysis for many years. It is noted, that, at the current state, own experimental work on detectability of genome-edited food or feed products of plant origin has not been conducted.

[12] Lusser, M., Parisi, C., Plan, D., Rodríguez-Cerezo, E. (2011) New plant breeding techniques. State-of-the-art and prospects for commercial development. Luxembourg, *Publications Off. Eur. Union*, 184 p. (https://publications.europa.eu/en/publication-detail/-/publication/12988d6d-c6a4-41b2-8dbd-760eeac044a7/language-en).

[13] Lusser, M., Parisi, C., Plan, D., Rodríguez-Cerezo, E. (2012) Deployment of new biotechnologies in plant breeding. *Nature Biotechnology* 30:231–239 (doi:10.1038/nbt.2142).

[14] Khatodia, S., Bhatotia, K., Passricha, N., Khurana, S.M.P., Tuteja, N. (2016) The CRISPR/Cas genome-editing tool: Application in improvement of plants. *Front. Plant Sci.* 7:506 (doi: 10.3389/fpls.2016.00506).

[15] European Court of Justice, C-528/16 - Judgement of 25 July 2018. See: http://curia.europa.eu/juris/document/document.jsf?docid=204387&mode=req&pageIndex=1&dir=&occ=first&part=1&text=&doclang=EN&cid=515140.

2 Terminology used in this document

The term **conventional GMOs** will be used throughout this report to refer to plant GMOs obtained by recombinant DNA technology and characterised by the presence of introduced DNA sequences from the same or other species in the final organism.

Genome editing, also called gene editing, is a group of new directed mutagenesis techniques that facilitate addition, removal, or alteration of DNA sequences at a specific location in the genome. This is mostly achieved with the aid of the cell's natural DNA recombination/repair system activated with the use of a site-directed nuclease (SDN), creating a double-strand DNA break at a defined location, a repair template sequence consisting of an added nucleic acid molecule (*e.g.* an oligonucleotide or longer nucleic acid sequence with partial sequence similarity to the target site), or the combination of both (modified from [8]). The techniques require the presence of the SDN in the recipient host cell, either following stable integration of recombinant DNA into the plant genome, or by transient expression or delivery of a protein/nucleic acid complex into the cell. In this document we will refer only to plant cells, but also other organisms could be targets of genome editing. When recombinant DNA has been used, it can be segregated away in subsequent generations, resulting in genome-edited plants that no longer contain any recombinant DNA[16,17]. In the frame of this report, plants obtained with genome editing techniques that contain inserted recombinant DNA or unintentionally remaining insertions of the transformation vectors are excluded, as these will be similar to the current conventional GMOs.

Early but limited success of genome editing was first achieved with protein-directed SDNs such as meganucleases, zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs). The techniques of genome editing have advanced rapidly following the development of RNA-directed SDNs based on the bacterial CRISPR (clustered regularly interspaced short palindromic repeats) system and CRISPR-associated (Cas) nucleases[8]. Editing of single nucleotides can also be achieved using a specific set of enzymes referred to as 'base editors', which aim at modifying DNA at specific sites without involving double-strand breaks[18].

The DNA sequence alterations introduced through any of the genome editing techniques may be single nucleotide variants (SNV), insertions or deletions (called InDels), or, less frequently, gene duplications, inversions and translocations[19]. 'Short' DNA alterations, as mentioned in this report, are referring to changes in one or a few base pairs, while 'large' alterations refer to alterations of several dozen base pairs. However, there is a grey zone between 'short' and 'large' sequence alterations. When talking about the specificity of detection, the criterion to be assessed is not the sequence length itself, but whether or not a given DNA alteration is unique or occurs already in any plant species, or potentially could occur, and whether or not it can be unequivocally attributed to the application of genome editing. This may need to be assessed on a case-by-case basis using approaches which should be defined by the ENGL.

By analogy to the term 'transformation event' used in GMO legislation[2], we propose here to use '**genome-edited event**' to refer to the altered DNA sequence, as indicated above, at a specific site in the genome as a result of the genome editing technique. A prerequisite is that no recombinant DNA remained in the genome of the final plant (from vector backbone or other 'unwanted' integrations), which was not removed by segregation. Furthermore, as genome editing may create several intended DNA

[16] Zhang, Y., Liang, Z., Zong, Y., *et al.* (2016) Efficient and transgene-free genome editing in wheat through transient expression of CRISPR/Cas9 DNA or RNA. *Nat. Commun.* 7:12617.

[17] Liang, Z., Chen, K., Li, T., *et al.* (2017) Efficient DNA-free genome editing of bread wheat using CRISPR/Cas9 ribonucleoprotein complexes. *Nat. Commun.* 8:14261.

[18] Zong, Y., Wang, Y., Li, C., Zhang, R., Chen, K., Ran, Y., Qiu, J.-L., Wang, D., Gao, C. (2017) Precise base editing in rice, wheat and maize with a Cas9-cytidine deaminase fusion. *Nat. Biotechnol.* 35:438-440.

[19] Zhu, C., Bortesi, L., Baysal, C., Twyman, R.M., Fischer, R., Capell, T., Schillberg, S., Christou, P. (2016) Characteristics of genome editing mutations in cereal crops. *Trends Plant Sci.* 22:38-52.

alterations in the genome simultaneously, each of these multi-edits, when segregating independently, would require a specific detection method.

The term '**detection**' as referred to in this report encompasses different aspects:

(1) the 'finding' of a target sequence, *i.e.* detection *sensu stricto*, without necessarily being specific for the genome-edited event;

(2) the identification of the detected sequence as a specific genome-edited event;

(3) and the quantification of the genome-edited event.

For feed and food marketing authorisation under the GMO regulations, all three aspects of the broader interpretation of 'detection', *i.e.* including quantification, need to be fulfilled as the detection method needs to be able to quantify the presence of the genome-edited event at the GMO labelling threshold for adventitious or technically unavoidable presence of authorised events (0.9 m/m % expressed in mass fraction per total mass of the ingredient or plant species). When GMOs with pending or expired authorisation status are detected in feed[5], it needs to be assessed if their mass fraction is below the minimum required performance limit (MRPL) of the analysis method (0.1 m/m %). Methods for the detection of unauthorised GMOs, however, do not, in principle, need to be quantitative or event-specific as detection *sensu stricto* is sufficient for assessing non-compliance of the product.

3 Validation of detection methods for genome-edited events under an EU authorisation request

3.1 Possibilities and challenges for analytical methods

In an authorisation context, the GMO producer applying for market authorisation (the 'applicant') of a GMO has to submit a complete dossier for risk assessment. This dossier shall include a detection, identification and quantification method, with supporting method performance data, and the reference material should be made available. Applicants should follow the guidelines publicly available to prepare the 'method validation dossier' (http://gmo-crl.jrc.ec.europa.eu/guidancedocs.htm). In the EU authorisation and control context, it is required that analytical methods are specific to unambiguously identify the GMO, that they provide a dynamic range around the labelling threshold (*i.e.* 0.9 m/m %), and that they reach the desired level of sensitivity, robustness, ease of use and accuracy of quantification.

At the time of writing, more than 150 applications for authorisation of mostly plant GMOs for food or feed uses have been submitted in the EU since the GM food and feed legislation came into force[2].

In most of these cases, the GMOs contained one or more inserted foreign DNA sequences of up to several thousand nucleotides long. The genetic transformation procedures employed for their generation have resulted in an 'event' of insertion of recombinant DNA sequences. For each insertion, two unique insert-to-plant junctions are generated, one at each end of the integration site. Each of the unique junctions created during a transformation event can be exploited as a unique identification marker for developing a method of detection specific for each conventional GMO (often referred to as 'event-specific' detection method).

Although genetic modifications may affect other classes of molecules such as RNA and proteins and gradually down to metabolites, which can all be targets of analytical methods, the benchmark technology for the analytical detection, identification and quantification of GMOs is typically based on real-time PCR (also called quantitative PCR or qPCR), a method widely used in molecular biology to target DNA molecules. This technology provides a million-fold amplification of a selected target DNA sequence of typically 70-150 base pairs, located across one of the insert-to-plant junctions. qPCR can provide high sensitivity and robustness for the precise relative quantification of GM material, even at low levels, in food and feed products. When qPCR is targeting the unique sequences of transformation events, it ensures the required level of specificity to be in compliance with the legal requirements.

The EURL GMFF validates the detection methods provided by applicants for market authorisation in an interlaboratory validation exercise involving National Reference Laboratories[20]. The ENGL guidance on minimum performance requirements[3] provides the reference basis for the assessment of the validation study. The validated quantitative method and certified reference materials (CRMs) for calibration and quality control of the method constitute a complete 'toolkit' for the unequivocal identification and quantification of a GMO[21,22].

In the frame of establishing this report, the scientific literature from different fields has been reviewed to evaluate if the current ENGL method performance criteria could be applied to methods for the detection and quantification of genome-edited products.

[20] Commission Implementing Reguation (EU) No 120/2014 of 7 February 2014 amending Regulation (EC) No 1981/2006 on detailed rules for the implementation of Article 32 of Regulation (EC) No 1829/2003 of the European Parliament and the Council as regards the Community reference laboratory for genetically modified organisms. *Off. J. Eur. Union* L39:46-52.

[21] Trapman, S., Corbisier, P., Schimmel, H., Emons, H. (2009) Towards future reference systems for GM analysis. *Anal. Bioanal. Chem.* 396:1969-1975.

[22] Corbisier, P., Emons, H. (2019) Towards metrologically traceable and comparable results in GM quantification. *Anal Bioanal. Chem.* 411:7-11.

It has been shown for SNV allelic discrimination assays developed in other domains[23,24] that quantitative parameters such as PCR efficiency, slope and linearity are in line with those established by the ENGL. Other assay types such as competitive allele-specific and RNase H2-dependent PCR-assays used for genotyping in plant breeding programs showed higher sensitivity and specificity in comparison to TaqMan assays[25]. However, in those studies the materials tested were of a lower complexity and consisted of individual genotypes and plants. Both the sensitivity of the method for a genome-edited product and its specificity are challenging issues for food and feed products with a complex composition.

The assays mentioned above and other strategies would require a significant level of method optimisation and experience which is currently not available. Moreover, such approaches need to be validated in interlaboratory studies to ensure transferability of the methods across laboratories, which has not been shown up to now.

Digital PCR (dPCR) methods have been used for the screening and confirmation of particular mutations in clinical samples, namely induced pluripotent stem cells or primary cells at very low concentrations[26,27]. In some dPCR assays[27] two probes, binding to the mutated or wild-type sequence, were used for the simultaneous quantification of both wild-type and mutated sequence copies from the same PCR amplicon. This substitutes the use of taxon-specific genes for relative quantification of the GM events as currently proposed in the ENGL document on Minimum Performance Requirements[3]. However, it should be noted that the samples analysed in these studies were of limited complexity, not comparable to samples of food and feed products from plants.

Other authors have compared the relative specificity and sensitivity of qPCR versus dPCR assays in detecting and quantifying SNVs or small InDels in individual founder transgenic mice generated by CRISPR/Cas9 mutagenesis: a lower rate of false-positive unedited events was observed when using a dPCR assay, and locked nucleic acid probes could be used to enhance the specificity of the assay[28]. Overall, the dPCR methods seem to be preferred in comparison to qPCR methods, however the precision, trueness and specificity of the methods have not been systematically evaluated for genome-edited plant products.

Theoretically, sequencing-based strategies, such as Next Generation Sequencing (NGS), could potentially be applied for the simultaneous detection of (multiple) genome edited events. On a case by case basis, target enrichment or probe capturing NGS approaches may be considered, for which a proof of concept has been reported for the detection of conventional GMOs[29,30]. The quality criteria to assess sequencing data are currently under

[23] de Andrade, C.P., de Almeida, L.L., de Castro, L.A., Driemeier, D., da Silva, S.C. (2013) Development of a real-time polymerase chain reaction assay for single nucleotide polymorphism genotyping codons 136, 154, and 171 of the *prnp* gene and application to Brazilian sheep herds. *J Vet. Diagn. Invest.* 25:120-124 (doi: 10.1177/1040638712471343).

[24] Feligini, M., Bongioni, G., Brambati, E., Amadesi, A., Cambuli, C., Panelli, S., Bonacina, C., Galli, A. (2014) Real-time qPCR is a powerful assay to estimate the 171 R/Q alleles at the *PrP* locus directly in a flock's raw milk: a comparison with the targeted next-generation sequencing. *J. Virol. Meth.* 207:210-4 (doi: 10.1016/j.jviromet.2014.07.017).

[25] Broccanello, C., Chiodi, C., Funk, A., McGrath, J.M., Panella, L., Stevanato, P. (2018) Comparison of three PCR based assays for SNP genotyping in plants. *Plant Meth.* 14:28 (doi: 10.1186/s13007-018-0295-6).

[26] Miyaoka, Y., Berman, J.R., Cooper, S.B., Mayerl, S.J., Chan, A.H., Zhang, B., Karlin-Neumann, G.A., Conklin, B.R. (2016) Systematic quantification of HDR and NHEJ reveals effects of locus, nuclease, and cell type on genome-editing. *Sci. Rep.* 6:23549 (doi:10.1038/srep23549).

[27] Mock, U., Hauber, I., Fehse, B. (2016) Digital PCR to assess gene-editing frequencies (GEF-dPCR) mediated by designer nucleases. *Nat. Protoc.* 11:598-615 (doi: 10.1038/nprot.2016.027).

[28] Falabella, M., Sun, L., Barr, J., Pena, A.Z., Kershaw, E.E., Gingras, S., Goncharova, E.A., Kaufman, B.A. (2017) Single-step qPCR and dPCR detection of diverse CRISPR-Cas9 gene editing events in vivo. *G3: Genes/Genomes/Genetics* 7:3533-3542 (doi: https://doi.org/10.1534/g3.117.300123).

[29] Fraiture, M.A., Herman, P., Papazova, N., De Loose, M., Deforce, D., Ruttink, T., Roosens, N.H. (2017) An integrated strategy combining DNA walking and NGS to detect GMOs. *Food Chem*. 232:351-358.

[30] Arulandhu, A.J., van Dijk, J., Staats, M., Hagelaar, R., Voorhuijzen, M., Molenaar, B., van Hoof, R., Li, R., Yang, L., Shi, J., Scholtens, I., Kok, E. (2018) NGS-based amplicon sequencing approach; towards a new era in GMO screening and detection. *Food Control* 93:201-210.

discussion, for instance at ISO level[31]. This should also contribute to establishing a framework for the validation of NGS-based methods in the future. It should be noted that NGS approaches are currently not sufficiently validated for the quantification of targets in complex mixtures.

Although it is technically possible to detect specific DNA alterations, without prior knowledge, none of the techniques described are able to distinguish whether the SNV or InDel is caused by genome editing, by classical breeding technologies or by natural mutation (see Chapter 3.2).

3.2 The event-specificity requirement of detection methods

Specificity is the property of a detection method to respond exclusively to the target of interest. Annex III to Regulation (EU) No 503/2013[32] states that *"the method shall be specific to the transformation event (hereafter referred to as 'event-specific') and thus shall only be functional with the genetically modified organism or genetically modified based product considered and shall not be functional if applied to other transformation events already authorised; otherwise the method cannot be applied for unequivocal detection/identification/quantification*."

For current transformation events, the method specificity is ensured by targeting the junction between the inserted transgene sequence(s) and the plant DNA, which is a unique identification marker created *de novo* upon the randomly inserted transgene sequence. Moreover, as it will be highly unlikely that exactly the same transgenic genome sequence will be created *de novo* a second time, this unique marker is also ensuring traceability to the process that generated the GMO, independent of further breeding activity to cross the GM event into different genetic backgrounds.

The situation is complex for genome-edited plants. First, in the absence of foreign DNA in the genome-edited plant, the altered sequence, whether short or long, may not necessarily be unique, *i.e.* the same DNA alteration may already exist in other varieties or in wild plants of the same or other species. For instance, in rice, targeted base editing technology was shown to create the same nucleotide alterations in the acetolactate synthase (ALS) herbicide resistance gene as known from natural varieties of rice and other plant species[33]. In other plants, genome editing has reproduced traits in elite varieties that exist already in wild plant species, and the corresponding DNA alterations may not be distinguishable[34,35].

Secondly, as a result of the ease of use and site-specificity of the genome-editing techniques, exactly the same DNA alteration may be created by different operators (companies, researchers) independently, in order to create plants with a desired phenotype such as disease resistance. If the DNA alterations are identical, it would be impossible to trace back by current state-of-the-art technologies the genome-edited event to a unique identification marker, developed by a specific company in a specific genome-editing experiment. The ownership of and liability for a genome-edited plant may therefore be unclear.

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[31] ISO/WD 20397-2 Biotechnology - General requirements for massive parallel sequencing - Part 2: Methods to evaluate the quality of sequencing data (https://www.iso.org/standard/67895.html).

[32] Commission Implementing Regulation (EU) No 503/2013 of 3 April 2013 on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006. *Off. J. Eur. Union* L157: 1-47.

[33] Shimatani, Z., Kashojiya, S., Takayama, M., Terada, R., Arazoe, T., Ishii, H., Teramura, H., Yamamoto, T., Komatsu, H., Miura, K., Ezura, H., Nishida, K., Ariizumi, T., Kondo, A. (2017) Targeted base editing in rice and tomato using a CRISPR-Cas9 cytidine deaminase fusion. *Nat. Biotechnol.* 35:441-445 (doi:10.1038/nbt.3833).

[34] D'Ambrosio, C., Stigliani, A.L., Giorio, G. (2018) CRISPR/Cas9 editing of carotenoid genes in tomato. *Transg. Res.* 27:367–378.

[35] Chilcoat, D., Liu, Z.B., Sander, J. (2017) Use of CRISPR/Cas9 for crop improvement in maize and soybean. *Prog. Mol. Biol. Transl. Sci.* 149:27–46 (doi: 10.1016/bs.pmbts.2017.04.005).

For market authorisation, applicants have to submit an event-specific detection method and demonstrate that the method is specific for the GMO. This would require full knowledge of all existing sequence variations for the genome-edited locus for all varieties and wild plants of all species used for food or feed production, which would serve as reference basis. At present, sequence databases compiling the sequence variation of all individuals of a species, *i.e.* the pan-genome[36,37,38,39], are being developed for several plant species (see Text box 2). In case of single nucleotide alterations it will be difficult or even impossible to guarantee that the same alteration is unique and does not exist in other varieties/populations, or will be created spontaneously or by random mutagenesis techniques in future plants. The same problem may exist in case of more than a single nucleotide alteration, and even for larger gene deletions or duplications that may exist already in conventional varieties[40]. If continuously updated pan-genome databases are not available, it may not be possible for applicants to demonstrate the uniqueness of the DNA alteration or for the EURL GMFF to verify this information and to conclude that the method submitted is event-specific.

Consequently, it could be difficult for applicants to develop an event-specific detection method for a genome-edited plant not carrying a unique DNA alteration. It will need to be assessed on a case-by-case basis if a given DNA alteration corresponds to a specific genome-edited event that can be targeted by a detection method fulfilling all minimum performance requirements, including specificity. It is currently unclear how this specificity could be assessed, both *in silico* and experimentally.

In conclusion, whereas the detection *sensu stricto* of genome-edited events may be technically feasible, the same specificity for identification as currently applicable to conventional GM event-specific methods may not be achieved in all possible cases. For methods targeting genome-edited plants, it cannot be excluded that the identical DNA alterations occurred already spontaneously, were introduced by random mutagenesis or were/will be created in an independent editing experiment. This uncertainty will have consequences for enforcement of the GMO legislation.

[36] Hirsch, C.N., Foerster, J.M., Johnson, J.M., Sekhon, R.S., Muttoni, G., Vaillancourt, B., Penagaricano, F. (2014) Insights into the maize pangenome and pan-transcriptome. *Plant Cell* 26:121–135.

[37] Li, Y.-H., Zhou, G., Ma, J., *et al.* (2014) *De novo* assembly of soybean wild relatives for pan-genome analysis of diversity and agronomic traits. *Nat. Biotechnol.* 52:1045-1054.

[38] Alaux, M., Rogers, J., Letellier, T., *et al.* (2018) Linking the International Wheat Genome Sequencing Consortium bread wheat reference genome sequence to wheat genetic and phenomic data. *Genome Biol.* 19:1-10.

[39] Zhao, Q., Feng, Q., Lu, H., *et al.* (2018) Pan-genome analysis highlights the extent of genomic variation in cultivated and wild rice. *Nat. Genet.* 50:278–284.

[40] Custers, R., Casacuberta, J.M., Eriksson, D., Sagi, L., Schiemann, J. (2019) Genetic alterations that do or do not occur naturally; consequences for genome edited organisms in the context of regulatory oversight. *Front. Bioeng. Biotech.* 6:213.

Text box 2

Variability of plant genomes

Advances in whole genome sequencing in recent years have revealed that the genome sequences of plant species are diverse and dynamic. Dispensable genes may constitute a significant proportion of the pan-genome, *e.g.* around 20 % in soybean[41]. A comparison between two maize inbred lines showed that their genomes contained respectively 3,408 and 3,298 unique insertions and deletions (InDels), with an average size of approximately 20 kbp (20,000 base pairs) and a range covering 1 kbp to over 1 Mbp[42]. Currently, comprehensive knowledge on the genomic variability among commercial plant varieties of agricultural crops is not available. Moreover, it remains unclear to what extent such information would provide a substantial contribution to the detection of genome-edited events, especially against the background of the high dynamics of plant genomes.

Spontaneous natural mutations are expected to change the genome at each reproduction cycle. For instance, there is a seven in 1 billion chance in the model plant Arabidopsis (*Arabidopsis thaliana*) that any given base pair will mutate in a generation[43], meaning that 175 new variants (SNVs) would arise per 100 individual plants per generation. In rice, more than 54,000 novel DNA sequence variants were identified in a line that went through *in vitro* culture (and 8 cycles of self-fertilisation), compared to the wild-type line, without showing any different phenotype under normal growing conditions[44]. The relatively slow rate of natural mutation has also been increased by several orders of magnitude by conventional mutagenesis, such as irradiation or chemical treatment of seeds or pollen, which have been applied in plant breeding for several decades[45,46]. Such mutant plants, which are exempted from the GMO regulations, have been incorporated in traditional breeding programmes and have contributed to the current crop diversity.

3.3 The minimum performance requirements for analytical methods of GMO testing

The European Network of GMO Laboratories (ENGL) elaborated in 2015 the third version of the guidance document on minimum performance requirements for analytical methods of GMO testing[3]. The document, inter alia, is addressed to applicants submitting detection methods according to Regulation (EC) No 1829/2003 and it provides criteria upon which methods for GMO detection are assessed and validated by the EURL GMFF. The ENGL document takes into account the requirements of the relevant international standards (ISO 24276, ISO 21569, ISO 21570, ISO 21571) and recommendations of the Codex Alimentarius[47].

Method validation is an essential component of the measures that a laboratory, operating its methods under accreditation to ISO/IEC 17025[48], shall implement before releasing test results. The standard requires that the analysis of a sample is performed by using 'validated' methods.

It is important to underline that the ENGL document refers to PCR-based methods since those are generally applied across applicants and control laboratories for GMO analysis. It details the acceptance criteria and performance requirements for 1) DNA extraction and purification methods, 2) PCR methods for the purpose of quantification and, 3) PCR methods for the purpose of qualitative detection (Table 1).

[41] Li, Y. H., Zhou, G., Ma, *et al.* (2014) De novo assembly of soybean wild relatives for pan-genome analysis of diversity and agronomic traits. *Nat. Biotechnol. 32:*1045-1052.

[42] Jiao, Y., Peluso, P., Shi, J., *et al.* (2017) Improved maize reference genome with single-molecule technologies. *Nature* 546:524-527.

[43] Ossowski, S., Schneeberger, K., Lucas-Lledó, J.I., Warthmann, N., Clark, R.M., Shaw, R.G., Weigel, D., Lynch, M. (2010) The rate and molecular spectrum of spontaneous mutations in *Arabidopsis thaliana*. *Science* 327:92-94.

[44] Zhang, D., Wang, Z., Wang, N., Gao, Y., Liu, Y., Ying, W., Yan, B., Zhibin, Z., Xiuyun, L., Yuzhu, D., Xiufang, O., Chunming, X., Bao, L. (2014) Tissue culture-induced heritable genomic variation in rice, and their phenotypic implications. *PLoS ONE* 9:e96879 (doi:10.1371/journal.pone.0096879).

[45] Jankowicz-Cieslak, J., Tai, T.H., Kumlehn, J., Till, B.J. (2016) Biotechnologies for Plant Mutation Breeding. SpringerLink ISBN 978-3-319-45019-3.

[46] Anderson, J.A., Michno, J.-M., Kono, T.J.Y., Stec, A.O., Campbell, B.J., Curtin, S.J., Stupar, R.M. (2016) Genomic variation and DNA repair associated with soybean transgenesis: a comparison to cultivars and mutagenized plants. *BMC Biotechnol.* 16:41.

[47] Codex Alimentarius Commission (2009) Foods derived from modern biotechnology. FAO/WHO, Rome, Italy.

[48] ISO/IEC 17025:2017, General requirements for the competence of testing and calibration laboratories. International Organization for Standardization, Geneva, Switzerland.

Table 1. Method acceptance criteria and performance parameters considered in the ENGL document on minimum performance requirements for methods of GMO testing (version 2015)[3].

Criteria	DNA extraction	Quantitative PCR	Qualitative PCR
Method acceptance criteria	Applicability Practicability DNA concentration DNA yield DNA structural integrity Purity of DNA extracts	Applicability Practicability Specificity Limit of Detection (LOD) Robustness Dynamic Range Trueness Amplification Efficiency R^2 Coefficient Precision Limit of Quantification (LOQ)	Applicability Practicability Specificity Limit of Detection (LOD) Robustness
Method performance requirements		Trueness Precision	False positive rate False negative rate Probability of detection

It should thus be considered to which extent the analytical methods proposed for genome-edited plants would (1) comply with the current provisions of the ENGL document as it is, and (2) if additional explanatory notes or amendments need to be made in order to provide a quality and compliance framework for analytical approaches not yet covered. The most critical aspects for consideration include the following elements:

- **Applicability/Practicability of the method**. For new technologies, *e.g.* next-generation sequencing, the equipment may not be widely available, the quality assurance parameters and uncertainty estimation are still under development, and training may be required in the enforcement laboratories to make sure the methods can be applied in a reliable way.
- **Specificity to be demonstrated *in silico* and experimentally**. In order to develop a detection method that is specific for identification of the genome-edited event, a unique and sufficiently long sequence is required. SNV and short InDels may not provide such a unique sequence. It also needs to be specified which databases and which plant samples have to be used for demonstrating the event-specificity of the method.
- **Robustness of the method**. It needs to be assessed whether methods targeting a SNV or short InDel are sufficiently robust against small modifications to the testing conditions.
- **Sensitivity (Limit of Detection/Limit of Quantification)**. Proof of evidence is required to demonstrate that a method targeting a SNV or short InDel has an acceptable limit of detection in different sample types.

Further considerations are necessary in order to provide guidance on the requirements for detection methods for genome-edited products containing multiple DNA alterations. A characteristic of genome editing techniques such as CRISPR-Cas and TALEN is the possibility to simultaneously modify all alleles of a gene or different genes simultaneously[49,50,51,52,53,54]. This may lead to plants having multiple alterations in their

[49] Wang, Y., Cheng, X., Shan, Q., Zhang, Y., Liu, J., Gao, C., Qiu, J.-L. (2014) Simultaneous editing of three homoeoalleles in hexaploid bread wheat confers heritable resistance to powdery mildew. *Nat. Biotechnol.* 32:947-952.

[50] Wang, Z.P., Xing, H.L., Dong, L., Zhang, H.Y., Han, C.Y., Wang, X.C., Chen, Q.J. (2015) Egg cell-specific promoter-controlled CRISPR/Cas9 efficiently generates homozygous mutants for multiple target genes in Arabidopsis in a single generation. *Genome Biol.* 16:144.

genome at one or more loci, which may be present in a homozygous or heterozygous state (*i.e.* all copies of the gene may have the same alteration or different alterations). Event-specific detection methods would be required to target all different alterations in the genome in case they may segregate in subsequent generations. Analysing the performance of multiple methods on a single genome-edited plant makes it more laborious for the EURL GMFF to perform the method validation in an interlaboratory trial and for the enforcement laboratories to carry out the verification of these methods when they are implemented in the laboratory. The case of multiple genome-editing events is to some extent similar to the detection of stacked transformation events in food and feed, with the difference that in the latter case, the regulatory approach demands the validation of a detection method for each of the single transformation events composing the stack, before the validation of the same methods on the stacked product can be started. For genome-edited plants, the 'single events' may not exist independently when multiple alterations have been created at once. Therefore, when two or more single genome-edited events belonging to the same ingredient are found in a food or feed sample, it cannot be concluded if these originate from a multi-edited plant or from segregated single-event plants.

[51] Miao, C., Xiao, L., Hua, K., Zou, C., Zhao, Y., Bressan, R.A., Zhu, J.-K. (2018) Mutations in a subfamily of abscisic acid receptor genes promote rice growth and productivity. *PNAS* 115:6058–6063.

[52] Yu, Z., Chen, Q., Chen, W., Zhang, X., Mei, F., Zhang, P., Zhao, M., Wang, X., Shi, N., Jackson, S., Hong, Y. (2018) Multigene editing via CRISPR/Cas9 guided by a single-sgRNA seed in Arabidopsis. *J. Integr. Plant Biol.* 60:376-381 (doi.org/10.1111/jipb.12622).

[53] Liang, Z., Chen, K., Li, T., *et al.* (2017) Efficient DNA-free genome editing of bread wheat using CRISPR/Cas9 ribonucleoprotein complexes. *Nat. Commun.* 8:14261 (doi.org/10.1038/ncomms14261).

[54] Peterson, B. A., Haak, D. C., Nishimura, M. T., Teixeira, P. J. P. L., James, S. R., Dangl, J. L., & Nimchuk, Z. L. (2016) Genome-wide assessment of efficiency and specificity in CRISPR/Cas9 mediated multiple site targeting in *Arabidopsis*. *PLoS ONE* 11:1–11 (doi.org/10.1371/journal.pone.0162169).

4 Detection of genome-edited events in the context of market control

Every day, shipments of thousands of tons are arriving at EU harbours where they await clearance for unloading the commodity. Verification of compliance with the EU food and feed legislation is achieved through a mixed system of document traceability and laboratory testing. According to EU legislation, accompanying documentation is provided with the indication on whether the lot contains GMOs or not. Moreover, custom inspectors collect and prepare a sample for laboratory analyses (controlling for GMOs, mycotoxins, heavy metals, pesticides, etc.) according to the applicable sampling schemes and recommendations.

Bulk grain that arrives in a harbour, and similarly any food or feed product produced from it, is a compound product composed of different source materials, including plant varieties with different genetic backgrounds, cultivated by various farmers in various regions of the world and present in different proportions. Samples taken from these products are analysed by the official control laboratories of the EU Member States for the presence of GMOs. Real-time PCR-based methods are well-established analytical techniques adopted by all control laboratories in the EU. Methods for detection need to be robust and applicable to the typical heterogeneous nature of food and feed samples tested by enforcement laboratories.

The current first-line approach employed by enforcement laboratories to analyse samples for the presence of GMOs is mainly based on an analytical screening strategy for common DNA sequences, such as gene promoters (*e.g.* CaMV P-*35S*), gene terminators (*e.g.* T-*nos*), or protein coding sequences (*e.g. cp4 epsps*, *pat* or *cry1Ab*) that are commonly found in authorised as well as in unauthorised conventional GMOs. These methods will react positively for all GMOs that contain the element-specific sequences.

Based on the outcome of the initial screening, the second step will be to test for the presence of authorised GMOs using event-specific methods, or for known unauthorised GMOs for which construct- or event-specific methods are available (http://gmo-crl.jrc.ec.europa.eu/gmomethods/). This strategy may lead to the direct detection of an unauthorised GMO (in the case of known unauthorised GMOs that may have been detected earlier), but it may also lead to the conclusion that some of the detected GMO screening targets could not be explained in this way. These unexplained elements may point indirectly at the presence of (additional) unauthorised GMOs in the sample. Subsequent research, for example using targeted or untargeted sequencing[55,56], is then required to elucidate the background of the identified GMO elements. In this way GMOs without an EU authorisation application, with or without prior information on the modification, may be detected insofar they contain a common screening marker[57].

For genome-edited plants such screening methods generally are not possible, as the plants considered in this report do not contain any transgene sequence nor any other common element that can be screened for. In the absence of targets that are common and therefore specific for a large group of genome-edited plants no general screening approach is applicable or can be developed. As a consequence, it can be asssumed that in the near future the distinction between detection by screening and subsequent identification may not be applicable as for conventional GMOs. Instead, detection and

[55] Košir, A.B., Arulandhu, A.J., Voorhuijzen, M.M., Xiao, H., Hagelaar, R., Staats, M., Costessi, A., Žel, J., Kok, E.J., van Dijk, J.P. (2017) ALF: a strategy for identification of unauthorized GMOs in complex mixtures by a GW-NGS method and dedicated bioinformatics analysis. *Sci. Rep.* 7:14155 *(*doi:10.1038/s41598-017-14469-8).

[56] Wahler, D., Schauser, L., Bendiek, J., Grohmann, L. (2013) Next-Generation Sequencing as a tool for detailed molecular characterisation of genomic insertions and flanking regions in genetically modified plants: a pilot study using a rice event unauthorised in the EU. *Food Anal. Meth.* 6:1718-1727.

[57] ENGL (2011) Overview on the detection, interpretation and reporting on the presence of unauthorised genetically modified materials. Guidance document of the ENGL. (http://gmo-crl.jrc.ec.europa.eu/doc/2011-12-12%20ENGL%20UGM%20WG%20Publication.pdf).

identification will coincide, as the detection of genome-edited events already requires targeting the unique sequence in the analysis.

Alternative approaches to PCR for the detection of unauthorised GMOs have been developed in recent years. Screening of market samples using NGS has been proposed by a few EU control laboratories for the detection of unauthorised GMOs[30,59,58]. It uses the known sequences of conventional GMOs (common elements or coding sequences of transgenes) as a 'bait' to detect both authorised and unauthorised GMOs in a market sample. This screening approach is dependent on the presence of combinations of foreign DNA sequences and cannot detect genome-edited events. As a consequence there are no robust laboratory methods to assure that unknown unauthorised genome-edited products could be prevented from entering the market.

If marketed genome-edited plants are not sufficiently assessed during development, unwanted transgenic sequences (*e.g.* vector backbone sequences) may potentially have remained in the genome in case the genome editing technique employed involved integration of the construct into the plant genome and it was not carefully segregated out in subsequent crosses[59,60,61]. This will require developing additional screening methods for the detection and as well the identification of such unintentionally remaining recombinant DNA sequences.

The implementation of methods for the detection of genome-edited plants in the process of an application for EU authorisation depends strongly on the prior knowledge of the sequence alteration and on the availability of reference material. Only if the analytical procedure for detection, identification and quantification of a genome-edited product has been found fit for the intended purpose by the EURL GMFF, then the validated method may be generally applied for control purposes. The genotype of such plant product from a homogeneous sample might be identified in a homogeneous (reference) sample. However, in heterogeneous samples (commodities) unambiguous detection of hidden admixtures and identification of individual genotypes will be not possible in most cases[62].

In the absence of a market authorisation request in the EU, some genome-edited plants may have been authorised in other markets, and information could have been published in patents and/or scientific journals. If the DNA alteration in such plants is known, and would be sufficiently informative to be targeted by a detection method, the application of such method, already published or to be developed, may allow detection of the genome-edited product. However, at the current state no assessment has been carried out for any method for the detection of any genome-edited plant product by the ENGL or the EURL.

The detection of very small sequence 'signatures' by bioinformatics and of genetic or methylation 'scars', as hypothesised recently[63], does not provide realistic evidence and proof that a new breeding technique was applied and has caused a detected DNA alteration. Signatures like the PAM sequence (PAM- Protospacer adjacent motif - a 2-6 bp

[58] Fraiture, M.A., Saltykova, A., Hoffman, S., Winand, R., Deforce, D., Vanneste, K., De Keersmaecker, S.C.J., Roosens, N.H.C. (2018) Nanopore sequencing technology: a new route for the fast detection of unauthorized GMO. *Sci. Rep. 8:7903.*

[59] Braatz, J., Harloff, H.J., Mascher, M., Stein, N., Himmelbach, A., Jung, C. (2017) CRISPR-Cas9 targeted mutagenesis leads to simultaneous modification of different homoeologous gene copies in polyploid oilseed rape (*Brassica napus*). *Plant Physiol.* 174:935-942.

[60] Li, W.X., Wu, S.L., Liu, Y.H., Jin, G.L., Zhao, H.J., Fan, L.J., Shu, Q.Y. (2016) Genome-wide profiling of genetic variation in *Agrobacterium*-transformed rice plants. *J. Zhejiang Univ. Sci*. B 17:992–996.

[61] Schouten, H.J., vande Geest, H., Papadimitriou, S., Bemer, M., Schaart, J.G., Smulders, M.J.M., Sanchez Perez, G., Schijlen, E. (2017) Re-sequencing transgenic plants revealed rearrangements at T-DNA inserts, and integration of a short T-DNA fragment, but no increase of small mutations elsewhere. *Plant Cell Rep.* 36:493–504.

[62] Grohmann, L., Keilwagen, J., Duensing, N., Dagand, E., Hartung, F., Wilhelm, R., Bendiek, J., Sprink, T. (2019) Detection and identification of genome editing in plants – challenges and opportunities. *Front Plant Sci.* 10:236 (doi:10.3389/fpls.2019.00236).

[63] Bertheau, Y. (2019) New Breeding Techniques: Detection and Identification of the Techniques and Derived Products. In: *Reference Module in Food Science, Encyclopedia of Food Chemistry, pp.* 320-336 (doi.org/10.1016/B978-0-08-100596-5.21834-9).

DNA sequence immediately following the DNA sequence targeted by the Cas nuclease) are relevant only for the CRISPR technique and vary depending on the type of Cas protein used. 'Scars' are potentially created in cells that have been directly treated by any mutagenesis technique or passed through tissue culture and are not exclusively induced by genome editing. Moreover, it is not clear to what extent epigenetic changes are stable across breeding generations.

The identification of DNA alterations from genome editing that are not unique remains, therefore, extremely difficult, as the altered sequences may mimic naturally occurring sequence variants, or they may not be distinguishable from those alterations obtained with conventional mutagenesis.

An alternative approach for the detection of unauthorised GMOs has been proposed in 2010, using documentation-based screening for products that potentially contain unauthorised GMOs. This is based on web crawling and text mining technologies using descriptive keywords, to be followed by analytical confirmation[64]. Such a laborious approach, if implemented by all actors in the field, could be considered as a way to collect world-wide information on the development and marketing of genome-edited plants, but it remains to be evaluated to what extent such an approach would be practical as it relies on open international collaboration, communication and voluntary exchange of information. Moreover, analytical confirmation for enforcement of the regulations would still be very challenging.

[64] Ruttink, T., Morisset, D., Van Droogenbroeck, B., Lavrac, N., Van Den Eede, G.L.M., Zel, J., De Loose, M. (2010) Knowledge-technology-based discovery of unauthorized genetically modified organisms. *Anal. Bioanal. Chem.* 396:1951-1959.

5 Conclusions and outlook

This report highlights analytical challenges and limitations related to the detection, identification and quantification of genome-edited food and feed products of plant origin.

Similarly to conventional GMOs, products of genome editing can only be readily detected and quantified in commodity products by enforcement laboratories if prior knowledge on the altered genome sequence, a validated detection method and certified reference materials are available.

The ENGL has issued a guidance document specifying the minimum performance requirements (MPR) of methods for GMO testing[3]. This document is informative for applicants submitting an event-specific detection method for a GMO as part of a request for market authorisation and provides the acceptance criteria for the EURL GMFF when validating the detection method. The document will need to be reviewed to clarify the implications for methods for genome-edited plant products. On the basis of the current knowledge and technical capabilities, it is unlikely that a method for a genome-edited plant product with only single nucleotide variations or short InDels would fulfil the performance requirements for methods of GMO testing, *e.g.* regarding applicability, sensitivity, specificity and quantification aspects.

The major bottleneck relates to providing proof for the origin of a detected DNA alteration, *i.e.* to be able to demonstrate that it was created by genome editing and refers to a unique genome-edited event that can be traced back to a specific genome-editing process. This may in principle be possible for unique DNA alterations, *e.g.* a large sequence deletion not mimicked by an identical alteration that has been identified already in the (natural) plant pan-genome. However, for non-unique DNA alterations affecting one or a few DNA base pairs, an applicant may not be able to develop an event-specific method.

In the absence of prior knowledge on the potential genome-edited alterations in a plant, their detection and identification by the enforcement laboratories does not seem to be feasible by using routinely applied detection methods and established analytical instrumentation. The general analytical screening strategy, as employed for conventional GMOs, cannot be applied for genome-edited plant products, as no common sequences are present that could be targeted for screening. In case a DNA alteration has been detected, there are currently no procedures established that facilitate an unambiguous conclusion that genome editing has created the alteration.

Therefore, plant products obtained by genome editing may enter the market undetected. Moreover, if a suspicious product with an unknown or non-unique DNA alteration would be detected on the EU market, it would be difficult or even impossible to provide court-proof evidence that the modified sequence originated from genome editing.

Several issues with regard to the detection, identification and quantification of genome-edited products cannot be solved at the present time, for example due to a lack of experimental verification, and will require further consideration. Technologies different from the currently applied qPCR methods may need to be implemented in the enforcement laboratories; additional resources will need to be made available and experience has to be developed. For known genome-edited events, alternative screening strategies targeting all known genome-edited events simultaneously may have to be developed to facilitate routine enforcement. Furthermore, under the current regulatory system the event-specific detection method is linked to a specific product application for market authorisation. However, the targeted mutagenesis techniques allow to reconstruct exactly the identical genome-edited product in another plant. Thus, the detection method for the food or feed product is no longer specific for the original genome-edited product, but would also detect the reconstructed product which has not received a market authorisation. The implications of this need to be further investigated.

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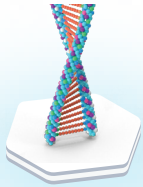
There are three types of advanced therapies:



Gene therapies

Cell therapies

Tissue-based therapies

Gene therapy alleviates the disease root cause or symptoms by replacing a malfunctioning gene or introducing a novel gene-based approach to help the patient return to good health. Gene therapies hold great potential for treating, preventing or curing a wide range of inherited conditions.

Cell therapy involves transforming cells in order to fight disease. Cells are adapted before being introduced into the patient's body where they target and treat diseased cells. The cells can be sourced from the patient's own body or from a healthy donor.

Tissue-based therapies seek to restore or replace damaged parts of the body through the combination of cells and active molecules. This aims to normalise the damaged cells' structure as much as possible. Such therapies may allow a tissue or organ to develop and grow inside the patient.

Where standard medical and surgical practice have not proved effective in curing or treating genetic diseases, advanced therapies emerge as a promising option for a potentially lifelong cure.

What advanced therapies are currently helping patients in the EU?

Here are some examples:

→ Patients with skin cancer and acute forms of blood cancer, such as leukaemia and lymphoma, are being treated by therapies which detect cancer cells and trigger the body's immune system to attack them.

→ Children with a rare inherited condition, causing their immune system to fail, are being treated by a therapy made from their own bone marrow.

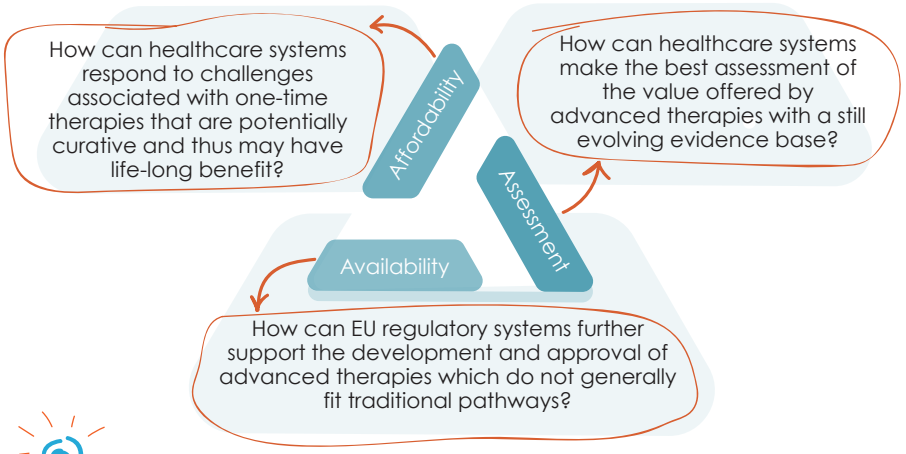
→ Patients who have been blinded through injury are having their sight restored by an innovative treatment using their own stem cells.

Since 2007 when the EU began to regulate advanced therapies, 14 advanced therapies have received marketing authorisation.

Advanced therapies that address the root cause of the disease with a one-time treatment can result in lower long-term costs for healthcare systems, compared to conventional treatments used for weeks, months, or even for life.

What are the challenges for the use of advanced therapies?

Advanced therapies represent a novel category of treatments and are often highly complex to develop and deliver. To fully maximise their potential, healthcare systems will need to adapt to ensure that patients across the EU can fully benefit. Advanced therapies pose new questions in three areas:



EuropaBio invites EU decision-makers to engage with us and our healthcare biotech members who are leading the field in advanced therapies.

We offer unparalleled knowledge and first-hand insight into the full range of issues relating to the pathway of innovative treatments from bench to bedside.

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12. Has there been any immediate impact on NGT-related research in your sector following the Court of Justice of the EU ruling on mutagenesis?

Court of Justice ruling: Case C-528/16 http://curia.europa.eu/juris/documents.jsf?num=C-528/16

- Yes
- No
- Not applicable

Yes. Together with Europe's scientific community, we regret that implementation of this ruling could cause European life science innovation effectively to come to a halt, as stated in EuropaBio's statement on the court ruling:
(Att. 5 & https://bit.ly/3cBB3oF)

We know of many examples of companies and public research organisations which have given up on their plans to bring genome edited products to the EU market for the foreseeable future, for example because public research grants were stopped in response to the court ruling.

As stated in EuropaBio's statement on the court ruling, *"If fast mitigation is not done, the ruling will cause a halt to EU sustainability and competitiveness ambitions by hindering the delivery of innovative bio-based products to the market, sustainable innovative food-solutions and certain healthcare solutions to patients,"* all the more since *"the EU has already fallen far behind the rest of the world in this essential area*".

Industrial Biotech:
The CJEU ruling emphasized the fact that the technology-based approach of Dir. 2001/18 is obsolete considering the innovation rate in modern biotechnology. Subsequent debates around the ruling made it clear that it would take a lot of efforts to modernize the legislation and facilitate global trade. This led to debates in the industrial biotechnology sector on whether it was still worth keeping R&D facilities and jobs in the EU, and developing and placing innovative products on the EU market.There was no immediate impact on the running business, as no NGT-derived product was developed and/or placed on the EU market under the assumption that it can be considered a non-GM product in the EU. Nevertheless, the ruling did have an immediate negative impact on innovation by preventing the pursuit of innovative concepts that would have benefitted both the conventional and non-GM markets. For some products intended for non-GM applications, industry needed to switch backto classical mutagenesis rather than using more appropriate genome editing approaches. In summary, the ruling prevented the use of innovative approaches of genome editing in some markets. One example is the potential use of genome editing in generating bacteriophage-resistant dairy cultures (Börner et al., FEMS Microbiol. Lett. 366:fny291, 2019; Stuer-Lauridsen & Janzen, European Patent No. EP 1 838 839 B1). As dairy cultures are traditionally a non-GM business, the "GM classification" of such phage-resistant strains plays an important role in determining market access and market success.

Agriculture technology companies voice intention to move R&D abroad: KWS seed company and HZPC, a Dutch trader in seed potato, confirmed that they will have to move part of their R&D outside Europe. The Dutch plant breeders' association Plantum confirms: 'As long as the new methods fall under the GMO legislation, companies based in the Netherlands will not invest in them, which puts their strong position in the global market at risk." According to Reuters, several agri-tech multinationals 'all but ruled out pursuing genetic plant breeding at home after the EU (ruling)'.

Research funding reduced: Research assignments are being withdrawn, reports Wageningen UR. In some Member States, public researchers reported an almost immediate cut of research funding for projects related to gene-edited crops, following the court ruling. In the majority of the (few) cases where field trials with gene-edited crops are taking place, these have been immediately required to come into compliance with GM legislation or preliminary decisions to regard those plants as non-GM plants were withdrawn.

Companies lose financing and put projects on hold: According to Nature, a Belgian start-up that planned to use CRISPR technology to help Africa's banana industry says it lost its financing, while a

company in Brazil says it has put millions of dollars' worth of gene-editing projects focused on soya beans on hold because its major market is in Europe.

EU funded research will not be utilized

Paradoxically, the EU has itself funded a wide range of research projects which involve CRISPR-Cas applications in e.g. agriculture and healthcare through several of its programmes (I.a. Horizon 2020, FP7, FP6, FP5 or the European Research Council). Within the agricultural scope alone, the total of these EU investments amounts to nearly € 27 million for 22 projects. For 148 projects related to healthcare applications, this even amounts to nearly € 197 million. With the CJEU ruling bringing these techniques under the umbrella of Directive 2001/18, institutions and companies in the EU are unlikely to reap the benefits of these tax-funded research projects.

Healthcare biotech:

Most of the clinical trials with medicinal products using NGTs (mutagenesis) techniques were initiated after the Court of Justice of the EU ruling on mutagenesis. Sponsors of these clinical trials comply with the GMO requirements as for any other gene therapies.

Statement: As EU court ruling risks blocking innovation, the European biotech industry calls for science-based political decision making on genome edited products

29 November 2018

The European biotechnology industry acknowledges with grave concern the EU Court ruling of 25 July 2018. This ruling interpreted the Annexes of the EU's Directive 2001/18 in such a way that organisms resulting from modern mutagenesis techniques are uniformly to be treated like genetically modified organisms[1].

Together with Europe's world leading scientific community in this field, we regret that implementation of this ruling could cause European life science innovation effectively to come to a halt[2]. If fast mitigation is not done, the ruling will cause a halt to EU sustainability and competitiveness ambitions by hindering the delivery of innovative bio-based products to the market, sustainable innovative food-solutions and certain healthcare solutions to patients. We, therefore, call on the EU Commission to thoroughly assess the consequences of the ruling, clarify the status of products made using other innovative approaches, and secure that Europe can benefit from modern precision editing methods.

EuropaBio firmly believes that, in order to advance the UN Sustainable Development Goals by 2030, a proportionate, fit-for-purpose and science-based approach to modern technologies, such as innovative biotechnology and life sciences, is essential. As a case in point, we regret that the lack of such an approach has already resulted in profound consequences for the adoption of environmentally and socially beneficial crops in Europe.

The EU's approval system for GMOs has prevented farmers from accessing products that have been used safely for decades in other parts of the globe and is so slow and expensive that even import authorisations represent an insurmountable hurdle for small and medium-sized companies and public institutions. Yet it is exactly these SMEs and publicly funded innovators who have the biggest share of genome-

[1] Court of Justice of the EU Ruling on Case C-528/16 and associated Press Release. EuropaBio Press Release.
[2] Position paper from 85 European plant and life sciences research centers and institutes, "Regulating genome edited organisms as GMOs has negative consequences for agriculture, society and economy", 24 October 2018. Statement of EU Commission's Scientific Advice Mechanism: "A Scientific Perspective on the Regulatory Status of Products Derived from Gene Editing…", 13 November 2018. For additional statements and context, see also EuropaBio website news item and EuropaBio's Green Biotech rEvolutions newsletter.

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edited organisms ready to offer to the market and will now likely be unable to do so in the EU. The result is that they will instead focus their research on other parts of the world, where these organisms are usually not treated like genetically modified organisms[3]. As such, the EU consistently undercuts its potential to compete in a global market and to reap the benefits of its own innovation in this field.

To prevent further attrition of biotech's potential to other regions and to boost EU's competitiveness and innovation, and reach the environmental and climate commitments, we call for a constructive change. Our goal is to obtain science-based, predictable and proportionate rules that reflect technical progress and that seek to ensure that organisms developed with more sustainable, precise, modern mutagenesis techniques are not subject to disproportionate regulatory requirements, when the very same products could also be obtained through earlier breeding or classical mutagenesis methods or could simply result from spontaneous processes in nature.

As the EU has already fallen far behind the rest of the world in this essential area of research and commercialisation, we hope that decision-makers in the Member States and at EU level will promote progress and innovation as a matter of urgency. Such an approach would be appropriately in line with President Juncker's plea not to "stifle innovation and competitiveness with too prescriptive and too detailed regulations"[4], as well as holding true to the European Council's demands for a future-proof and technology-neutral better regulation approach[5].

About EuropaBio

EuropaBio, the European Association for Bioindustries, promotes an innovative and dynamic European biotechnology industry. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a biobased and zero-waste economy. EuropaBio represents 78 corporate and associate members and bio regions, and 15 national biotechnology associations in turn representing over 1800 biotech SMEs. Read more about our work at www.europabio.org.

[3] As of August 2018, in the USA alone, 15 gene-edited plants and 1 gene-edited mushroom were considered as non-regulated. Of these 16 products which are non-regulated in the USA: 7 are from medium to large private companies not including the four multinational companies which hold most GMO authorisations; 6 are from public research institutions; 3 are from multinational companies. Source: Julius Kühn-Institut: 1. Aktualisierung der Übersicht über Nutz- und Zierpflanzen, die mittels neuer molekularbiologischer Techniken für die Bereiche Ernährung, Landwirtschaft und Gartenbau erzeugt wurden (Version 20.09.2018)

[4] "A New Start for Europe: My Agenda for Jobs, Growth, Fairness and Democratic Change Political Guidelines for the next European Commission" (2014)

[5] Research and Innovation friendly regulation - Council conclusions (adopted on 27/05/2016): http://data.consilium.europa.eu/doc/document/ST-9510-2016-INIT/en/pdf

Who benefits from intellectual property rights for agricultural innovation?

The Case of Ogura Oilseed Rape in France

Commissioned by:

8 October 2015, final report
(update of the original report, launched at November 2014)

Authors:

steward redqueen

Contents

About Steward Redqueen

Company profile
Steward Redqueen is a strategy consultancy firm that aims to make business work for society. It is represented in Amsterdam, Barcelona and New York and executes projects around the world. As specialists since 2000, Steward Redqueen focuses on integrating sustainability, quantifying impact and facilitating change for (multinational) corporations, (development) financial institutions and public sector organisations.

Socio-economic impact assessments (SEIA)
In the long run, business cannot succeed in societies that fail or fail to share the fruits of economic growth. The private sector therefore must include societal interests in its decision making and look for shared benefits. The better stakeholders understand how the private sector contributes to economic development, the more they will support its strategic goals. Steward Redqueen quantifies direct and indirect socio-economic impact in a particular country or region and analyse the myriad of ways through which firms are connected to the economy.

The Authors
René Kim is founder and partner of Steward Redqueen. He has worked with many multinational companies and private equity funds in both developed and emerging markets. Previously, he worked for the Boston Consulting Group in Amsterdam and as an academic at the Massachusetts Institute of Technology. He holds a cum laude PhD in Hydrology and Meteorology and is the author of many academic articles. Willem Ruster, is a senior consultant at Steward Redqueen and has worked for 15 multinational companies and organizations on more than 30 individual projects. Sabine Dankbaar is a consultant at Steward Redqueen and worked on SEIA projects for several (multinational) companies.

Prof. Ethan B. Kapstein is an associate partner of Steward Redqueen. He is also visiting fellow at the Center for Global Development and senior director for research at the McCain Institute for International Leadership, both in Washington, DC and a visiting researcher at Princeton University. For many years he held the chair in political economy at INSEAD, and has taught as a Visiting Professor at Wharton, Georgetown, and Oxford.

Track record
Steward Redqueen has completed more than 100 socio-economic impact studies and evaluations for multinational mining companies, development finance institutions, multinational food & beverage firms, agricultural companies, banks and recreational organisations, in Asia, Africa, North & South America and Europe.

About Crop Life International

CropLife International (CLI) is a global federation representing the plant science industry. On the industry's behalf, CLI address international developments in crop protection and agricultural biotechnology.

CLI promotes approaches that enhance sustainable agriculture in the interests of farmers, consumers and the environment. CLI aims to provide transparent information to its stakeholders and welcomes open dialogue with parties interested in the future of food and farming.

CLI is committed to supporting the safe and responsible use of the industry's products in order to provide a secure, varied, healthy and affordable diet for consumers.

The activities are financed by its member associations and research and development-driven member companies.

About EuropaBio

EuropaBio is the European Association of BioIndustries, and was created in 1996. Our members are involved in research, development, testing, manufacturing and commercialisation of biotech products and processes in human and animal healthcare, diagnostics, bioinformatics, chemicals, crop protection, agriculture, food and environmental products and services. EuropaBio also counts a number of National Biotech Associations in its membership who in turn represent more than 1800 biotech SMEs. The member companies active in agricultural biotechnology are BASF, Bayer, Dow Agro-Sciences, Keygene, KWS, Limagrain, Monsanto, Pioneer Dupont, Syngenta.

Executive summary

This study examines the case of Ogura oilseed rape technology in France. Ogura is a patented hybridisation technology developed by the French public research institute INRA that is used to make Oilseed Rape (OSR) hybrids with higher yields. The first hybrid seeds based on the Ogura innovation were introduced in 2000 and resulted in rapid adoption by farmers over the last decade. This technology is available on the market through non-exclusive licenses to several seed companies for which INRA receives royalty income.

Agricultural innovations are necessary to increase farmer productivity and global food supply. But research & development (R&D) require substantial investments and costs. Without the opportunity to recoup investments, limited resources are allocated to agricultural innovations. Over the last decades, Intellectual Property Rights (IPR) provided market protection to innovators and increased the incentive for R&D investments by enabling innovators to recoup investments, to generate income for shareholders and to fund new R&D. This legal environment stimulated R&D investments and the introduction of innovations, which have spurred agricultural productivity and food supply significantly.

However, IPR in agriculture are increasingly being questioned in society because some argue that it allows developers to extract too much profit at the cost of consumer. There is thus a trade-off between the need for R&D investments to produce new innovations (future benefits) and the distribution of the benefits from existing innovations to users and society (present benefits). Against this background EuropaBio and Crop Life International commissioned Steward Redqueen to develop an economic framework to analyse the socio-economic effects and the economic logic of IPR in agriculture.

Research in this area has so far focused on the partitioning of benefits once an innovation is available in the market and only qualitatively described the importance of the innovation incentive. The analysis in this report is an effort to include both perspectives and the trade-off between current and future benefits. A framework is developed that compares IPR regimes based on *the probability of innovations happening (the incentive)* and *the consumer benefits once an innovation is available in the market*. This framework has been applied to the development and adoption of Oilseed rape hybrids developed by using the Ogura technology (‘Ogura hybrids) in France and compares the actual situation (non-exclusive use of IPR) with exclusive use of IPR and a situation without IPR.

The results of this economic study show that:

- Even under favourable market conditions (increasing crop prices), it took INRA and seed companies approximately 15 years to recover their R&D investments;
- The Ogura hybrids have been adopted by 83% of farmers and will have delivered a projected € 1.0 billion economic benefit over the patent life;
- About 50% of this total economic benefit accrues to farmers and 25% further downstream towards processors and end consumers of livestock products.
- Most likely all downstream benefits will trickle down to the consumer over time

The report also examines the influence of the strength of IPR through economic modelling of what would have happened had Ogura hybrids been commercialised *either* without competition through exclusive use of patents *or* under full competition without an IPR system. These results show that the decision for an IPR regime involves a trade-off between current and future benefits:

- Whether or not certain processes and products are protected by IPR, pricing power of seed producers is constrained by the presence of alternatives and the heterogeneity of farmer preferences;
- In the case of Ogura, it can be heuristically argued that deviating from the non-exclusive use of patents would have reduced societal benefit:
    - In the absence of IPR the total societal surplus would have increased slightly by € 16 million (+10%), but it would have been rather unlikely that Ogura would have been developed – at least by a private sector company – because of the inability to recoup the investment as the innovator surplus would have vanished;
    - Exclusive use of patents would result in lower societal benefits of € 46 million (-39%) in exchange for a somewhat higher probability of innovations happening because innovator benefits would increase by € 11 million (+31%);
    - In other words, a small increase of (hypothetical) societal surplus would have eliminated the incentive to innovate whereas a modest increase of the incentive would have come at considerable societal cost.
- Even in the case of exclusive use of patents, farmers (and parties further downstream) would still receive at least 60% of the total economic benefits.

Finally, the report indicates some other socio-economic effects of Ogura:

- Using the same resources, Ogura led to 320,000 tons extra OSR production in France without additional resource use. This translates into a reduction of 66 kg carbon per ton OSR;
- In 2012, € 123 million extra farm benefits resulted into almost 1,200 jobs.

General Lessons

1. Intellectual Property Rights are essential to enable innovation by providing innovators the ability to recoup investments and fund new R&D.

2. Stronger IPRs increase the probability of innovations happening.

3. Most of the social welfare coming from patented innovations accrues to farmers and further downstream towards processors and end consumers, which, in the case of Ogura, is about four times higher than what accrues to the technology developer and seed companies combined.

4. The market power of an agricultural technology is primarily determined by the ability to increase performance (in this case yields) and not by the strength of its IPR.

5. Even when IPR are used exclusively, the pricing power of a seed producer is constrained by the presence of alternatives and the heterogeneity of farmer preferences.

6. The absence of IPR would have a considerable cost for society since the key innovation incentive would be eliminated and thus the chance of new innovations happening and their economic benefits would be significantly reduced.

Key Figures of the Ogura case

€ 1.0 billion	societal benefits during the Ogura patented life
75%	of societal benefits accrue to farmers and consumers
15 years	to obtain break-even for technology provider INRA and seed producers
320,000 tons	annual extra Oilseed Rape production by using Ogura hybrids without extra use of resources
€ 123 million	extra farm income from the use of Ogura hybrids in 2012
83%	adoption level of Ogura hybrids by farmers in 2012

1. Introduction

1.1 IPR in general

Many advances in society are made through innovation, the act of developing a new idea that can be applied to the resolution of a technical or market problem via an improved process or product. Innovation is the task of converting inventions into marketable products or technologies and making them available to a user.

Protection of intellectual property aims to encourage developers to innovate. IPR encompass any new creation which is given the legal status of property and grants developers a certain degree of protection from market forces, thereby enabling them to appropriate a part of the economic benefits resulting from adoption of the innovation. IPR are 'rights given to persons over the creations of their minds' and can be divided into the areas 'industrial property' (including trademarks and patents) and 'copyright'.[1] The importance of these rights was first recognized in the Paris Convention for the Protection of Industrial Property (1883) and the Berne Convention for the Protection of Literary and Artistic Works (1886).[2]

According to a joint study of the European Patent Office (EPO) and the Office for Harmonization in the Internal Market (OHIM), IPR-intensive industries contributed 26% of employment and 39% of GDP in the EU during 2008-2010. These shares are somewhat higher in the EU than in the US where IPR-intensive industries contribute 19% to employment and represent 35% of GDP. The World Intellectual Property Organization (WIPO) has identified several reasons to promote and protect IPR: innovations in technology and culture generate progress for and well-being of humanity; IPR protection creates a financial incentive to invest in innovation as it secures a return on investment for a considerable term; and IP intensive industries fuel economic growth and create jobs.[3] However, critics have argued that strong IPR can impede competition and prevent progress because IPR would lead to excessive power for inventors (allowing them to charge prices far higher than under full competition) and thus limiting the adoption and diffusion of new technologies and production methods. Moreover, 'patent trolls' may distort the market and 'patent thickets', a web of overlapping patent rights, make it difficult to market a new technology. An optimal IPR system should balance the incentive to innovate and the costs of these inefficiencies.[4]

1.2 IPR licensing

Technology licensing has been and will continue to be an essential mechanism to enable a return on investment and the sharing of benefits between research institutions and companies, as well as between companies. Once a patent is filed, an institution or company may commercialise the innovation itself, or market the innovation to potential licensees, or a combination of both. This allows the inventor to create a revenue stream and recover funds that were used in the product's development phase.

Based on the exclusive rights conferred by a patent, licensing is a permission granted by the patent owner to another to use the patented invention on agreed terms and conditions, including payment of a certain fee, while the patent owner continues to retain ownership of the patent. Here, the patent owner has the opportunity to transfer its rights to the licensee(s) through exclusive or non-exclusive licensing.

Licensing not only creates an income source for the patent owner, but also establishes the legal framework for making the innovative technology available to a wider group of researchers within institutions or companies, who may, in turn, further contribute to the development of the technology concerned.

1.3 IPR and innovation in agriculture

Farmers face the challenge of producing larger quantities of food while preserving and protecting natural resources. New technologies over the past century have enabled farmers to meet the needs of a growing population. This agricultural innovation process often requires significant research and development (R&D) investments that may or may not produce technologies that can be commercialised.

IPR has been used in agriculture to stimulate R&D investments by providing market protection in order to recoup investments. Part of the ensuing higher profits are reinvested into research and development (R&D) to produce the next round of new products that benefit farmers, consumers and the environment.

Five well known examples of IPR protected innovations are introduced here:

1. In *mechanisation,* the first patent was granted in 1886. Tractors are one of the great labour-saving innovations of the 20th century.[5]
2. The first patent for *synthetic fertiliser* was granted in 1911. Synthetic fertiliser supplies nutrients essential for the growth of plants. Fertiliser use can increase crop yields up to 30 to 50%.[6]
3. In the *crop protection* area, the first fungicide patent was granted in 1934. Such products protect crops against diseases, insects and weeds. By reducing pest pressures, crop protection products cut global crop losses in half each year.[7]
4. A revolutionary *drip irrigation* method that provides water directly to the roots of a plant through a tube system was patented in 1963. Used on more than 6 million hectares around the globe,[8] drip irrigation increases yields potentially by up to 50%.[9]
5. Since 1992, when the first *plant biotechnology* patent was granted, genetically modified (GM) seeds have been developed that enable:
    - Higher farmer income due to lower expenditure on inputs and higher output per hectare;
    - More efficient use of inputs (water, energy, etc.);
    - Nutritional benefits of vitamin-enhanced varieties and lower "bad" fat oil profiles.[10]

1.4 The need for IPR to enable agricultural innovation

The adoption of innovative crops is considered to have been the most rapidly adopted agricultural innovation since the invention of the plough.[11] It has transformed farming and plays an important role in driving long term productivity and sustainability in agriculture. GM crops are planted and replanted on more than 1.5 billion hectares cumulatively since 1996 and on 13% of global arable land in 2013; biotech crops have added € 75 billion to global farm incomes.[12]

The plant science industry is one of the world's most R&D-intensive industries. It ranks in the top four global industries in terms of percentage of revenues invested into R&D. For example, the industry's top 10 companies annually invest about € 1.69 billion – or 7.5% of sales revenue – into new product development.[13,14]

The cost of discovery, development and authorisation of a new plant biotech trait is estimated at over € 100 million.[15] Whereas historically most agricultural research was funded from public sources, the private sector has become the dominant player since the first biotechnology patent was granted in 1992. Currently the private sector is responsible for most of the global crop R&D expenditure[16]. The ability to protect IPR has increased the ability of technology developers to recoup their investments and to generate a profit. This in turn has spurred private sector investments in additional agricultural innovation.

The optimal IPR use depends on the technology and the market environment. Within agriculture, IPR essentially consists of patents, plant variety rights (PVR) and trade secrets. Trade secrets seem less suitable for protecting products sold on the open market due to the possibility of replication through reverse engineering.[17] PVRs only protect new varieties, which meet certain conditions, as a whole, in specific territories and during a defined time span. They do not protect specific plant characteristics ("traits"). The patent system, on the other hand, protects specific innovative technologies and traits in exchange for the full public disclosure of the invention, which brings new scientific information into the public domain. This disclosure is important as it induces further improvements of prior innovations and additional innovations.

However, the need for patent protection of agricultural innovations is increasingly being questioned by civil society. Pressure is increasing to limit the scope of patent protection for agricultural innovations or to exclude patentability of these innovations altogether. An important driver of this resistance is the fact that once a new technology exists (ex-post) a patent causes developers to set prices higher than under free competition.[18] This is seen by many as allowing developers to extract (too much) profit at the expense of the consumer. But the innovation would likely not have existed without an incentive for the upfront (ex-ante) investment of the developer. In other words; a trade-off exists between the ex-ante and ex-post interest of society.[19]

A patent is a social contract between society and innovators. Society accepts short term exclusive rights, in order to enable long-term social welfare through innovation. But it is clear that this social contract breaks when either society denies profits to risk-taking innovators or developers benefit too much from the protection granted to them.

1.5 Research objective

The objective of this research is to develop an economical model for the socio-economic framework to analyse the trade-off between:

a. The need for IPR to encourage R&D investments to generate new seed technologies driving future benefits for society;
b. The influence of IPR on the partitioning of economic benefits stemming from new seed technologies over seed companies and farmers driving current benefits for society;

The framework is applied to the case of Ogura hybrid rapeseed technology in France.

2. Framework

The framework mentioned in the research objective essentially ties together the ex-ante and ex-post perspectives on patents: the developer needs a guarantee that he can appropriate a sufficient part of the potential future benefits of a new technology as an incentive to invest in R&D. Society has a dual objective: on the one hand, it wants to maximize the probability of innovations happening, which means incentivising innovators. On the other hand, it wants to maximise the consumer benefits coming from the new technology once it is commercially available.

Agricultural research so far has focused mainly on the partitioning of benefits once an innovation is commercially available; it only qualitatively describes the importance of the innovation incentive. This analysis pioneers an approach to describe both perspectives and the trade-off between current and future benefits.

The framework in Exhibit 1 shows the trade-off between these two perspectives. Stronger IPR increase the incentive to innovate (and thus the probability of innovations happening) but tends to decrease the share of the benefits for consumers whereas the opposite is true for weak IPR.[20] From a value chain perspective it is important to note that consumer benefits initially consist of farmer income but some of these benefits may leak away to the end consumer (i.e. on and post farm benefits). The producer benefit (i.e. total benefit minus farmer benefit) is shared between technology developer, seed producer and seed distributor.

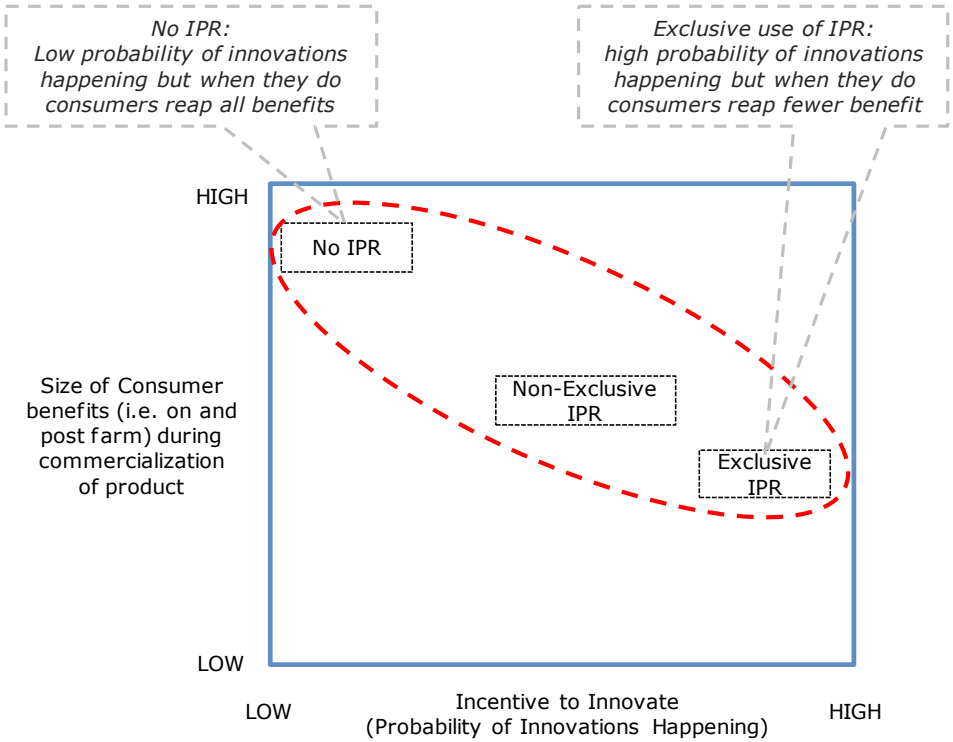

Exhibit 1: *Trade-off between consumer benefits and agricultural innovation incentives under different IPR regimes. Note that the location of the IPR regimes are highly indicative since they depend on local legislation.*

The three IPR regimes are indicatively shown in Exhibit 1: No IPR, Non-Exclusive use of IPR and Exclusive use of IPR. Table 1 describes the effects of these regimes in more

detail on consumer benefits (ex-post) and the incentive to innovate (ex-ante). As mentioned in Section 1.3, the optimal IPR regime depends on the innovation and the market circumstances.

IPR regime	Effects on (ex-post) consumer benefits	Effects on (ex-ante) incentive to innovate
No IPR	• Free technology allows for free competition and maximises consumer benefits vs other IPR regimes	• No market protection for innovator eliminates incentive for private R&D investments
Non-Exclusive use of IPR	• Competition on the market as seed producers can access technology through license fee • Lower consumer benefits vs no IPR due to license fee	• IPR provide higher incentive vs no IPR • Non-exclusive use of IPR lowers incentive vs exclusive use of IPR
Exclusive use of IPR	• Exclusive use of IPR provides most market power for innovator which lowers consumer benefits of current technology	• Most market power through exclusive use of IPR maximises incentive vs other IPR regimes

Table 1: *Effects of IPR regimes on (ex-post) consumer benefits and (ex-ante) incentive to innovate*

This report analyses the adoption of the hybrid Ogura rapeseed technology in France along the lines of the framework. The Ogura technology is an example of a non-exclusive IPR case as INRA grants non-exclusive licenses on its patented technology to seed producers. In addition to the observed partitioning of economic benefits the report also describes what would have happened under no IPR and exclusive use of IPR.

3. Background Ogura and Oilseed Rape (OSR) in France

3.1 Ogura hybrid technology can improve crop yield by 6-10%

The hybrid Oilseed Rape (OSR) introduced in the French market is based on the OGU-INRA technique, developed by the French National Institute for Agricultural Research (INRA). INRA is a public research institute with a € 882 million budget in 2012, ranking among the top 1% most-cited research bodies worldwide. In 2013, INRA had almost 500 plant variety certificates filed and owned 289 patents.[21]

The hybridisation of OSR is an example of a process innovation, as it is essentially a new production method. It enables combining traits of parents of two different varieties, which means that the offspring can show better performance than the sum of both. With these techniques seed companies can speed up genetic progress, ensure a better regularity of production and improve agronomic performances, like yields and characteristics of the product.[22] Hybrid seeds are considered one of the main contributing factors to the dramatic rise in agricultural output during the last half of the 20th century and are today the norm in many crops. However, the offspring seeds of hybrid crops will not consistently have the desired characteristics and farmers therefore repurchase seeds every growing season. This provides an effective protection for the seed producer.

INRA's development of the Male Cytoplasmic Sterility technology (CMS, also known as OGU-INRA) was a breakthrough in the hybridisation process of OSR. This led to the marketing of the first seed variety of hybrid OSR in 1994. As this first generation hybrid seed (based on 1991 patents) were associated with high Glucosinolate (GSL) values which can have negative side effects on human and animal health, further research was desirable. In 2000, the second generation hybrid seed (based on 1991 and 1996 patents), which could be considered the second generation of improved hybrids, reached the market with low GSL. A third generation of hybrid incorporating improved fertility restorer with better agronomics characters (based on 1991, 1996 and 2000 patents) were launched in 2008.[23]

This study focuses on the use in France of second generation Ogura hybrids, which on average improve yields by 6-10% according to academic research.[24] Exhibit 2 shows that after slow adoption until 2006, the uptake of the technology in France went fast and culminated in an 83% market share in 2012. It will be shown later that this uptake pattern was driven by the increase of earnings per hectare, which depends on yield increase, the market prices for the crop and the cost of the hybrid seed. For the 2nd generation hybrids, the 1991 patents represent the crucial breakthrough, but the 1996 patents made the innovation commercially viable and provided the ability to recoup the R&D investments (see Section 4.1).

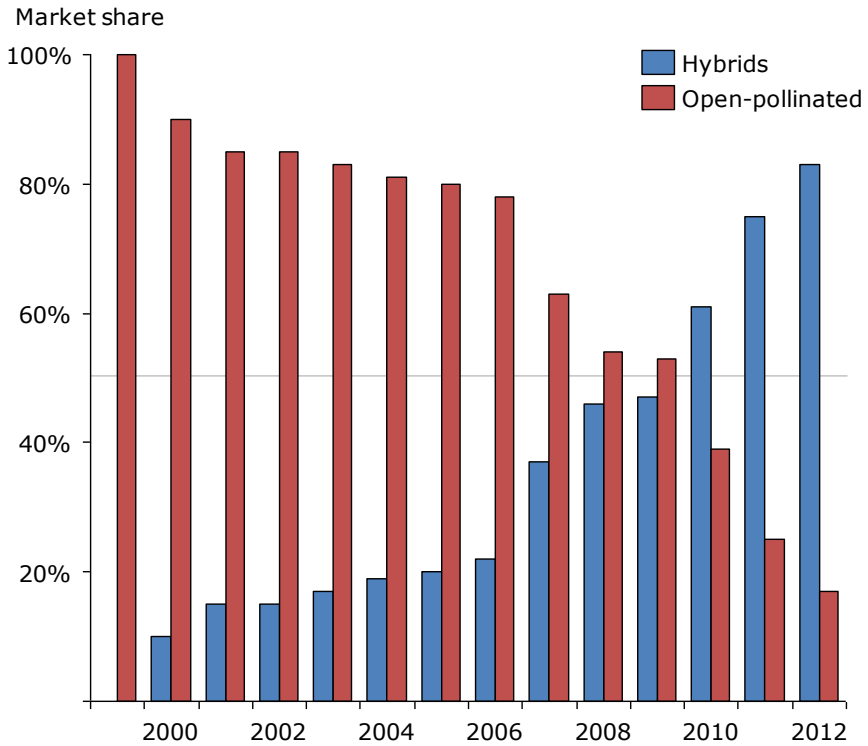

***Exhibit 2**: Observed market share of Ogura in France from 2000-2012*[25]

3.2 INRA grants non-exclusive licenses on patented technology to seed producers

Broadly, five stages can be distinguished in the R&D of an agricultural innovation: discovery, proof of concept, early development, advanced development, and pre-launch. In the hybridisation process of OSR, INRA was responsible for the discovery and partly

for proof of concept. INRA built a pool of all patents needed to develop Ogura hybrid varieties[26] through the acquisition of required patents it did not hold itself. In this way, INRA served as one-stop-shop for a bundling of Ogura technology. The patents were made available by INRA through non-exclusive licenses, which maximises the Freedom to Operate (FTO) for seed companies. Exhibit 3 provides an overview of R&D phases with estimations of the cost involved.

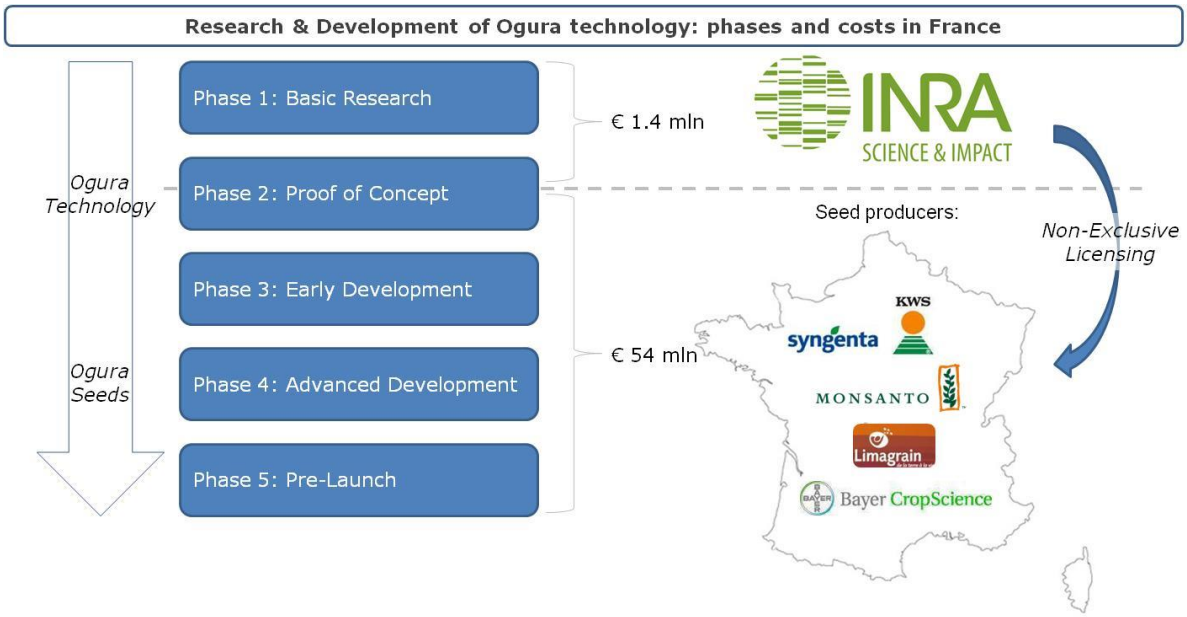

Exhibit 3: *R&D phases and their estimated costs for Ogura Hybrid technology in France*[27]

By obtaining a non-exclusive license, seed companies can use the technology to further develop different Ogura Hybrids. As shown in Exhibit 3 this seed development requires substantial investments from the proof of concept to the pre-launch phase. To increase the likelihood that companies would indeed make these investments, the patent licence agreement is structured as a royalty on the actual revenues rather than as an upfront license fee. Effectively, the royalty was 5% of the seed revenue generated until 2011 and 1% thereafter until 2016. Without going into detail on the many consortia and co-operations that have taken place, one can say that in Europe about five or six large companies have taken all the necessary steps to introduce commercial seeds. Up until 2011 this has produced € 50 million of global income for INRA, which lowers its dependency on government subsidy. Of these, € 14 million have been generated in France and relate to 23 varieties that have been introduced in this market since 2000.

3.3 France is among the largest producers of Oilseed Rape

Over the last decades, demand for Oilseed Rape has increased rapidly. The most common uses of OSR are oil for food and biodiesel and animal feed (as a by-product). Although, use of OSR for food purposes decreased slightly in Europe, the demand for it as a biofuel has increased exponentially. In Europe, OSR is the most important raw material used in biodiesel. Together, the countries of the European Union are the largest OSR producer worldwide, followed by Canada, China and India respectively. Within the European Union, France is largest producer, accounting for about 9% of global production

and 26% of European production.[28] Within France, OSR production is concentrated in the Centre and North.

In France, the OSR price increased since 2000 from € 185 per tonne and peaked in 2012 with € 479 per tonne, which made its cultivation more attractive for French farmers. Moreover, this price increase has made the switching to the higher yielding hybrids more attractive. Exhibit 4 shows that, consistent with the greater adoption of hybrid seeds, the average yield trends upward, although year-to-year variation is significant. Based on the previously mentioned 6-10% yield increase of hybrid seeds and the market share shown in Exhibit 2, we estimate that roughly half of the higher yields per hectare come from the adoption of hybrid seed. Similarly, the land used for OSR production increased with more than 30% (see Exhibit 4). Because 2.1 kg of seed per hectare is needed, the market size for OSR seed was about 3.3 million kg in 2012.[29]

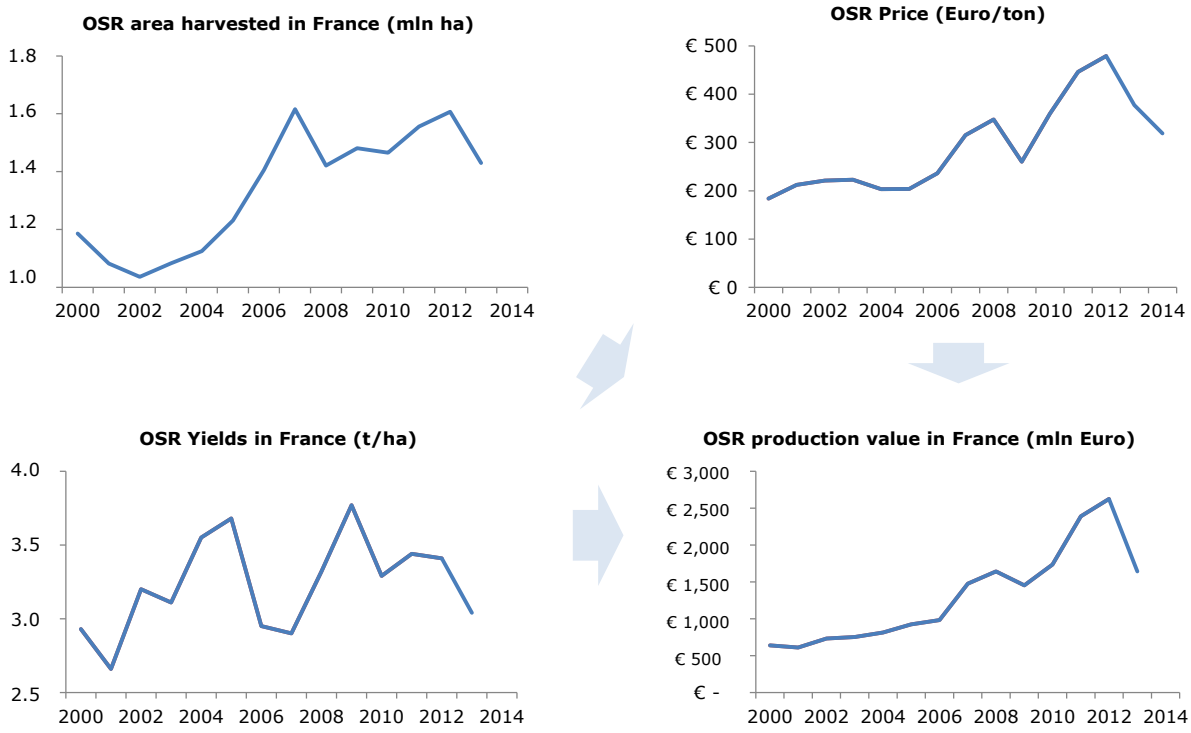

Exhibit 4: *Oilseed Rape (OSR) production info in France*[30]

4. Economic logic of IPR: economic benefits and benefits division of Ogura

Ogura technology provided € 1.0 billion of total economic benefit in France, while the licensing of patents provided the innovator INRA the opportunity to recoup investments. Section 4.1 gives more insight in the break-even points for INRA and the seed producers. Section 4.2 describes the partitioning of total economic benefits over the various actors.

4.1 Break-even point is about 15 year for seed companies and longer for INRA

INRA licensed the Ogura technology to seed companies during the final research phase. Exhibit 5 shows the license income of INRA globally. INRA's initial research on Ogura began in the 1980s, and came to its break-even point in 2006. This break-even point has

been made possible by the patent(s) on the technology. Here, the 1991 patents represent the breakthrough of the Ogura technology. However, the innovation would not have been commercially viable in combination with the 1996 patents. Exhibit 5 illustrates the long lead times for this innovation: two decades to break even followed by a short period during which profits are made.

Most of INRA Ogura income was generated up until 2011 when its key 1991 patents, which carried a royalty of 4%, expired. The other patents, for which it receives a 1% royalty, will expire in 2016.[31] Although one may conclude that the research institute has profited handsomely from the Ogura technology, one has to remember that in principle these profits have to cover the R&D cost of technologies that did not reach the market as well as fund the future R&D project pipeline. An industry survey in 2011 indicated most units that are tested during the discovery phase of the R&D process will never be introduced in the market place.[32] And, even under favourable market conditions (increasing crop prices), it took INRA still 15-20 years to recover their R&D investments.

Essentially, the economic outcome for INRA means that for every success (e.g. Ogura), 12 equally costly R&D projects could fail. According to INRA's financials about 80-90%[33] of its total license income comes from Ogura, which underscores that the technology's success is more of an exception than the rule. Of course, INRA is largely public funded and one may argue that it would not stop research in absence of IPR. However, INRA's use of patents lowers its dependency on government subsidy. Furthermore, most agricultural research is nowadays done by private institutions which need revenues to fund new R&D. When a private company cannot recoup its R&D investments it will most likely not invest. An top of that, it would expect a sufficient ROI that is competitive with other investment opportunities.[34] Therefore, the R&D investments and agricultural innovations would decrease significantly without IPRs.

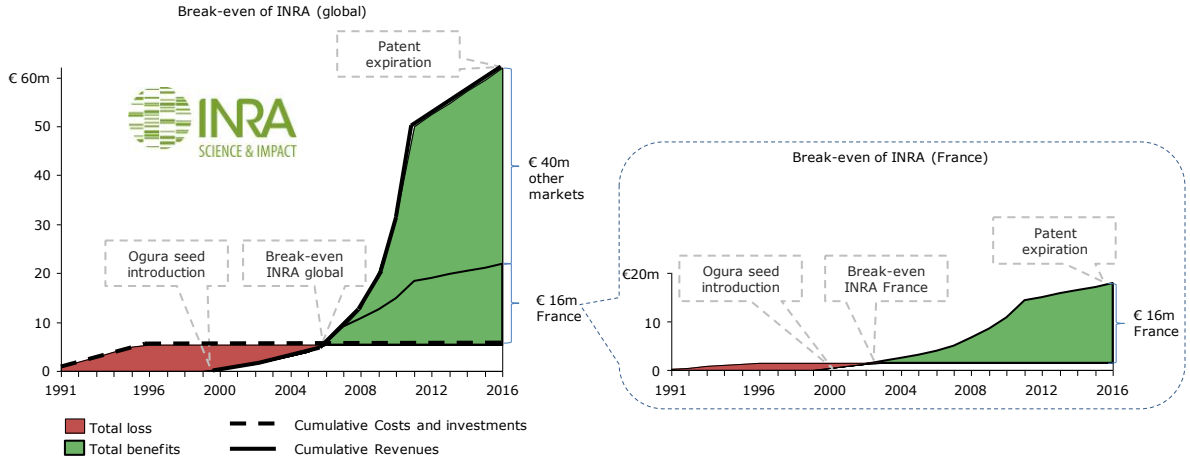

Exhibit 5: *Break-even point of Ogura for INRA, global and in France. An estimated 30% of Ogura's license income is originating from the French market (€ million, nominal)*

Seed companies signed the first licence agreements for Ogura technology in the mid-1990s. In order to make the early stage technology commercially viable, seed companies together spent approximately € 54 million to introduce commercial Ogura varieties in France in 2000.[35] It took until 2010, ten years after market introduction, to recoup these investments as shown in Exhibit 6. This would have been longer under less favourable development of OSR crop prices. For instance, the break-even point would roughly be 3-4 years later (i.e. 2013-2014) when OSR prices would not have increased after 2005.[36]

Some of the ensuing profits are reinvested into research and development (R&D) to produce the next round of new products.

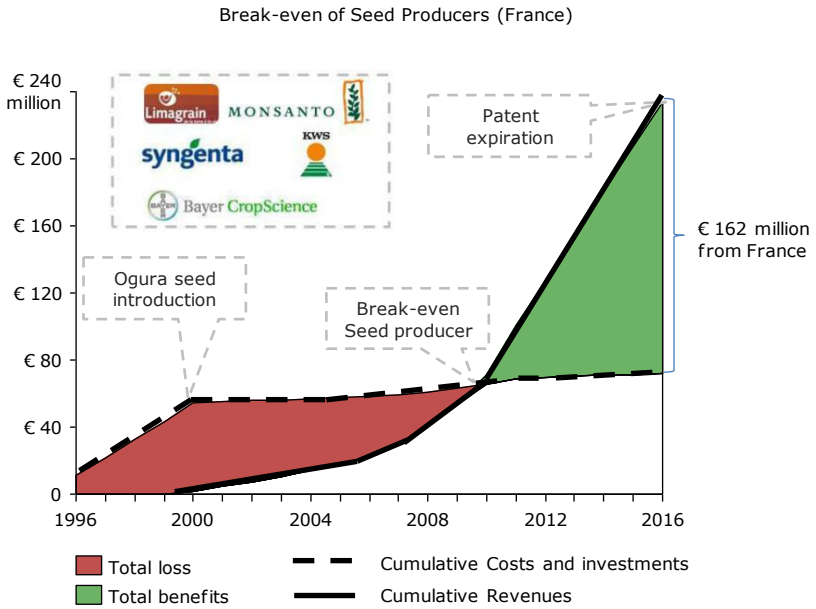

Exhibit 6: *Break-even point of Ogura for seed producers in France (€ million, nominal)*

Farmers that switch to Ogura hybrids do not need to change their operations. Thus as long as the yield increase and prevailing crop prices compensate for the higher seed costs, farmers turn a profit from the first year (see also Exhibit 8). In 2012, the extra costs for Ogura hybrids represented only 1% of farmer revenues while providing an extra 6-10% extra revenues. The adoption of Ogura hybrids is furthermore reversible; farmers can switch back to open-pollinated seeds ('lignées'), or adopt newer and better seeds for that matter, at any point in time.[37]

4.2 Projected economic benefit Ogura over patent life is € 1.0 billion

As shown in Exhibit 2, Ogura hybrids had captured 83% of the OSR seed market in France in 2012. The estimated total benefit created by Ogura over the full patent life is estimated to be € 1.03 billion as shown in Exhibit 8 and over time in Exhibit 8. Most of this benefit, about € 0.77 billion or 75%, goes to the farmers and downstream processors and consumers. Exhibit 7 presents the land use for OSR farming in 2012 and indicates that a large share of the on-farm benefits lands in the central and northern part of France.

From 2000 to 2014, farmers have spent a premium of € 235 million on Ogura hybrids relative to open-pollinated seed. Of this € 54 million (23%) accrued to seed distributors, 165 million (70%) to seed producers and € 16 million (7%) as royalty income to technology provider INRA. When assuming that the adoption of Ogura increases yield with 8%, the associated increase of farmer revenue is € 865 million. Therefore, total farmer benefits up until 2012 are € 631 million (i.e. € 865 - € 235 million).

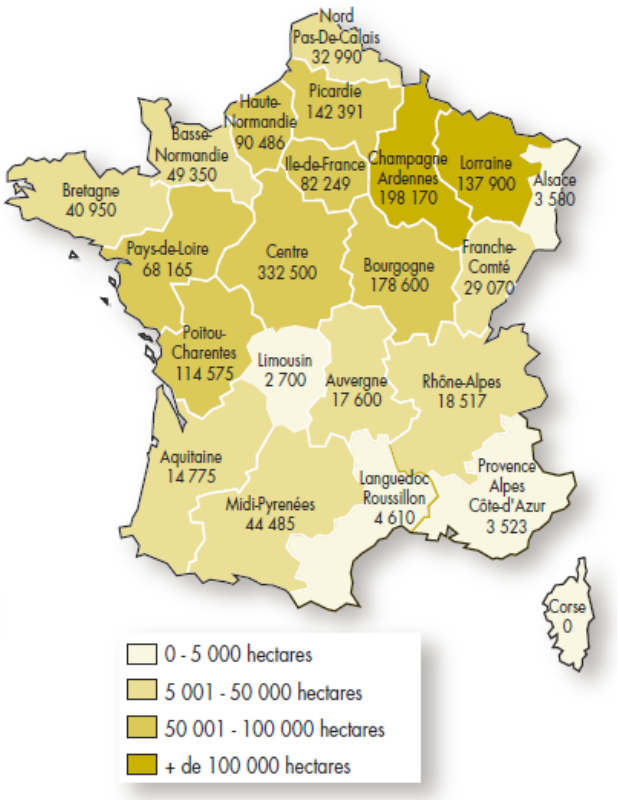

Exhibit 7: *Land use in hectare for Oilseed Rape farming in France, 2012 (Prolea 2013)*

Exhibit 3 summarises the R&D investment of INRA and seed producers, respectively € 1.4 million and € 54 million. By subtracting the investment costs from the extra revenues one arrives at € 110 million net benefit for seed producers (€ 164 million - € 54 million) and € 15 million for INRA (€ 16 million - € 1.4 million). The total realised economic benefit from inception to 2014 sums up to € 818 million. Assuming that the adoption rate remain at their 2012 level we project another € 210 million economic benefit until 2016, when the patent expires. Exhibit 5 summarises the partitioning of € 1,028 million economic benefit over the patent life. About 75% of the total economic benefit is captured by farmers, although it may well be that a part of this 'leaks' away to end consumers because of the lower crop prices due to larger production (see also Section 4.3). Other research on agricultural innovation suggests that once yield-increasing technologies (such as Ogura) is adopted more widely, most benefits in the long run will be gained by the end-consumer.[38]

One could also speak about the societal break-even point. In other words, at which point in time do the cumulative benefits of all parties involved in the chain match exactly their total costs. In the Ogura case, this point occurred around 2004 and is basically a weighted average of INRA, seed producer and farmer break-even.

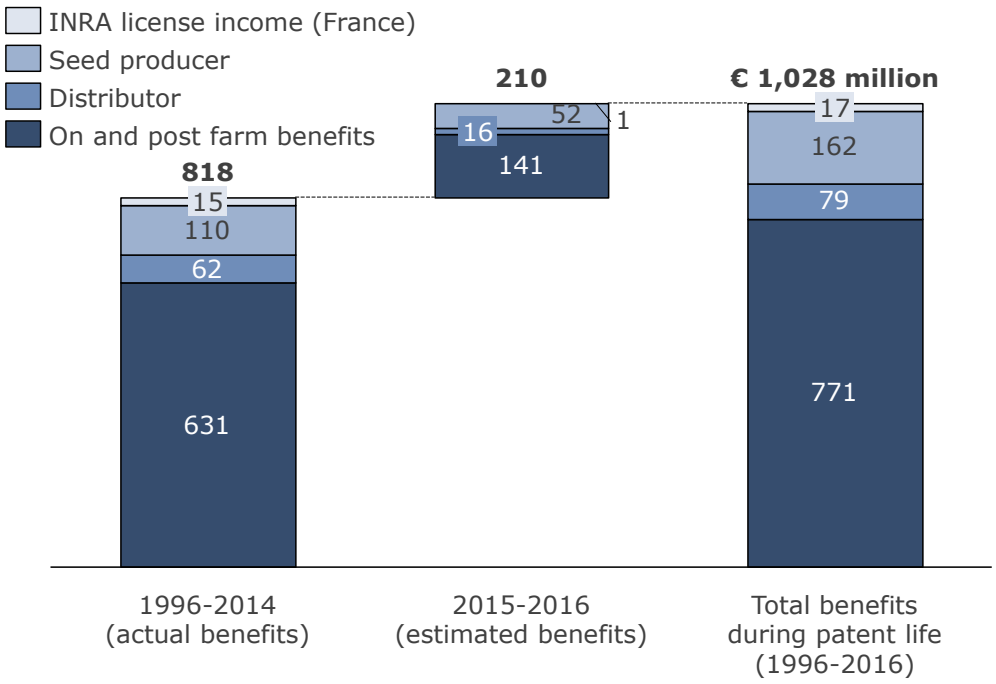

Exhibit 8: *Ogura economic benefits in supply chain during patent life, € million nominal (for estimated benefits for 2015-2016 constant 2014 crop prices have been assumed)*

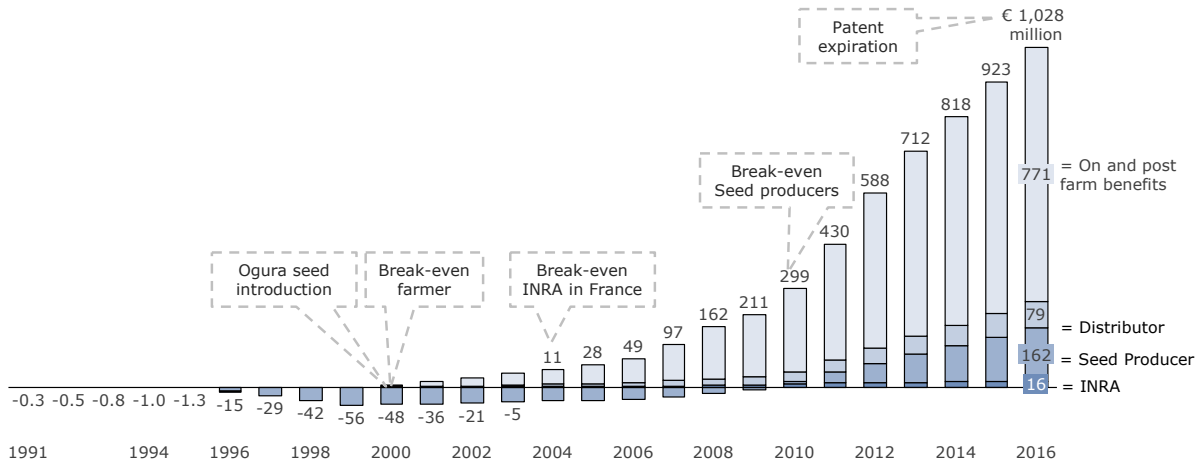

Exhibit 9: *Total benefits of Ogura for INRA, seed companies, distributors and farmers (i.e. on and post farm benefits) in France, 1991-2016 (€ million, nominal)*

To summarise this Ogura case: the technology provider (patent holder) and seed companies take considerable investment risk which took about 15 year to recoup. In return they receive about 25% of the total economic benefits. On the other hand, farmers receive 75% of the benefits while facing a limited financial risk. For INRA, the recovery of investment has been made possible through granting licenses on its patented technology to several seed companies.

4.3 Breakdown of on- and post-farm benefits

This section elaborates on the division of the *actual* on and post-farm benefits (€ 631 m 2000-2014, see Exhibit 8-9) up to the consumer. First, the estimated split between on and post-farm is shown and subsequently we indicate to what extent the post-farm benefits are likely to trickle down to the consumer.

Exhibit 10 summarises the value chain of rapeseed. Rapeseed is mainly used for crushing to produce rape oil for food and fuel purposes. During this process, an important by-product is produced: protein-rich rape meal which in Europe is an alternative for imported soy meals. Every 2.4 ton rapeseed produces 1.4 ton meal and 1 ton oil.[39] Rape oil prices are typically five times higher than its meals.[40]

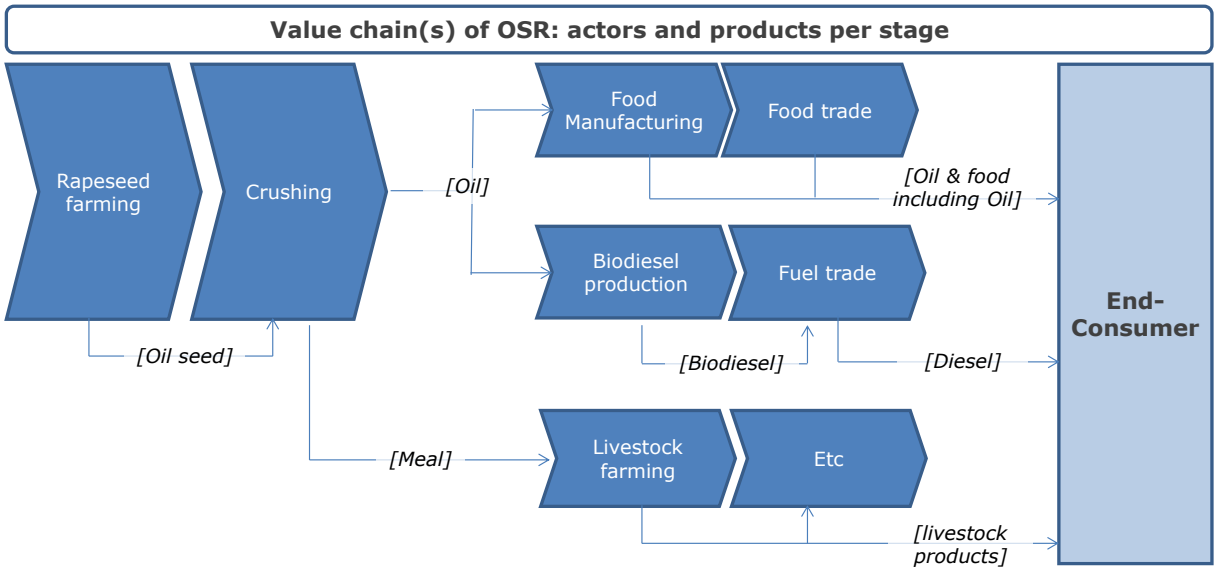

Exhibit 10: *The value chain of rapeseed*[41]

Over the full patent life, Ogura supports an increased production of some three million tons of rapeseed in France. According to FEDIOL, all extra rape oil in EU since 2003 is used for biodiesel production (see Exhibit 19 in Appendix III.3). Therefore, we assume that the extra rapeseed is crushed into oil used for biodiesel production, while its by-product rape meal is supplied to livestock as feed to substitute imported soy meals.

Typically, a change in supply in agro-commodity markets is met with a significant price response (USDA, 2014). However, rapeseed is clearly a fuel crop, especially in Europe where in 2012 two-third of its oil was used for biodiesel.[42] Therefore, price effects of Ogura-related extra production will have a smaller price effect in comparison with non-fuel crops, as its price is pre-dominantly set by the fuel price and biofuel quota.

In the early years after introduction, there was no price change related to Ogura because adoption was still limited and pre-dominantly in France. After 2007, adoption in and outside France rose sharply and as consequence extra rapeseed supplies related to an estimated price decrease of € 6 per ton after 2011 (see Appendix III.4).

These price effects translate into a shift of € 203 m from on to post-farm. These originate from both adopting and non-adopting farmers as prices affect all farmers. During 2000-

2014, it is estimated that € 489 m benefits remain on farm for hybrid farmers, while other farmers who did not adopt hybrid seeds lost € 62 m (see Exhibit 11).

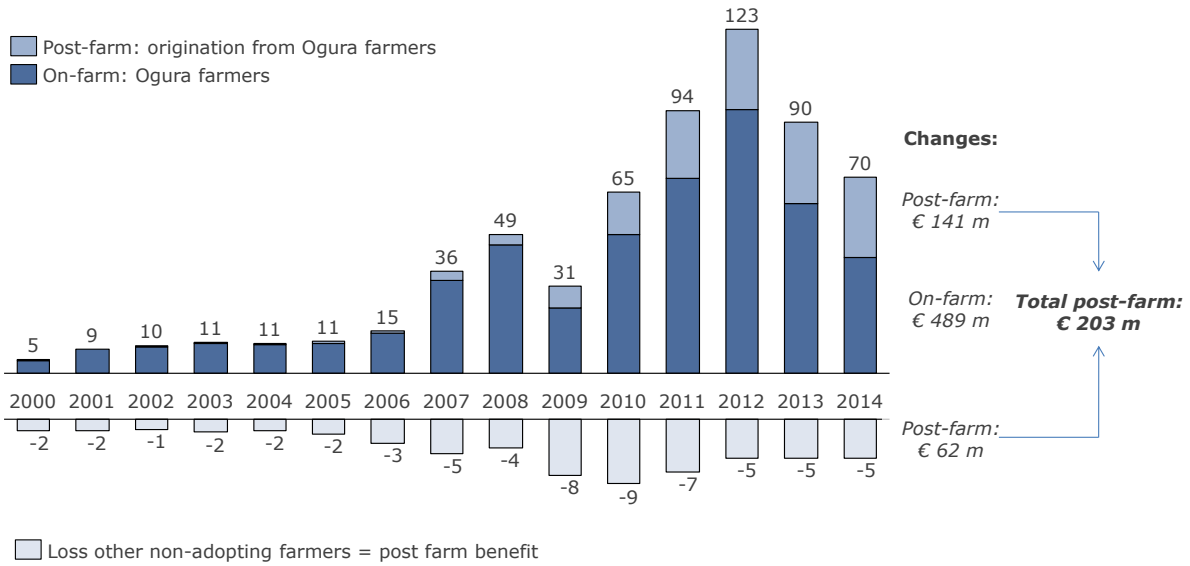

Exhibit 11: *Shift from on to post-farm benefits per year during 2000-2014 (€m)*

Exhibit 12 summarises the farmer benefits that relate to the extra yield and the shift in benefits from adopting and non-adopting farmers to post-farm. Here, we take the € 631 m (2000-2014, see also Exhibit 8) as starting point, which are the estimated farm benefits based on historical data. Subsequently, the price decrease results in € 141 m loss for hybrid (Ogura) farmers and € 62 m for other farmers using open-pollinated varieties, shifting € 203 m to post-farm (1/3 share of total).

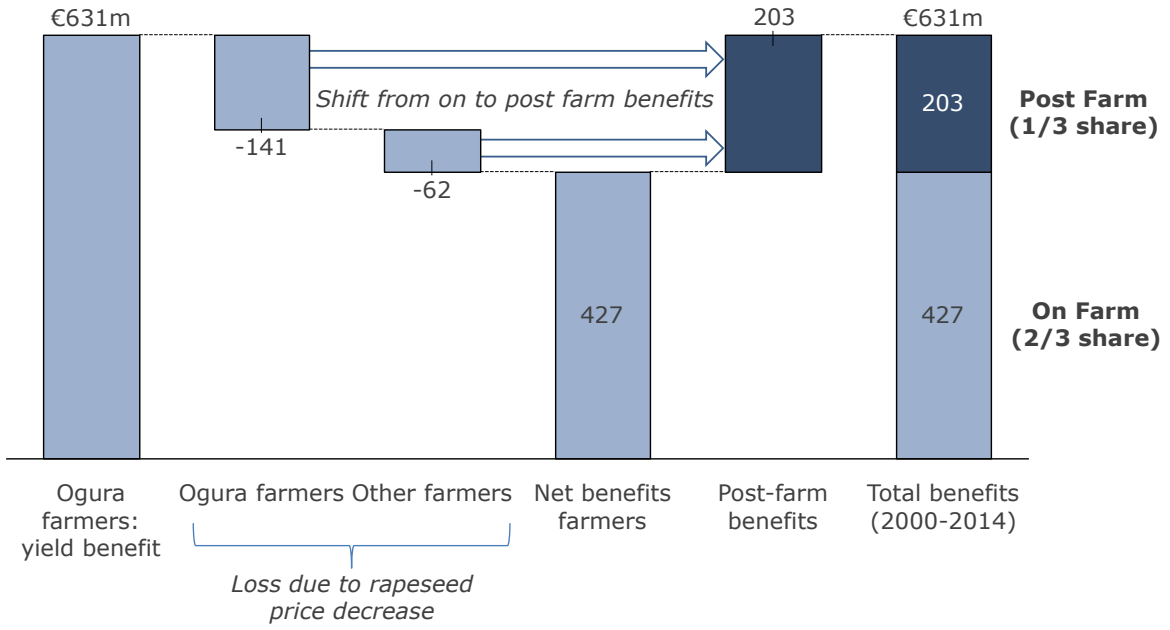

Exhibit 12: *On-farm benefits related to yield increase and benefit shift to post-farm related to price during 2000-2014 (€m)*

Knowing the estimated size of post-farm benefits, the question remains to which extent these trickle down to the consumer and for which products. There are no expected price changes for rape oil and biodiesel due to the nature of this chain. Oil demand for fuel use is highly elastic and therefore prices will hardly change when more rape oil is produced. However, more rape oil production provides also more rape meal to the market which demand is much more inelastic (i.e. significant price response). Therefore, rape meal prices will decrease and so will rapeseed prices as a consequence. This means that the post-farm benefits almost completely trickle down through the chain of livestock products and its producers and consumers.

The EC food price monitoring reports indicate that (processed) crop and feed prices typically travel down to the consumer with delay.[43] Also the analysis from CEREOPA and LEI-Wageningen University indicate that a change in protein-rich feed cost will most likely result in a change in consumer prices for milk and meat.[44]

Building on this research, it is expected that most of the € 203 m post-farm benefits will trickle down to the consumer in the short-term. However, feed costs are just a small portion of the consumer prices of livestock products, which will therefore have just a minor price effect per product.[45] In other words, the € 203 m is spread among many consumers.

5. Effects of IPR strength

In this section we consider how the distribution of economic benefits would have changed had Ogura been commercialised *either* without competition through exclusive use of patents *or* under full competition without an IPR system. In terms of Exhibit 1, we aim to analyse the difference between the exclusive (i.e. a stricter IPR regime), no IPR and non-exclusive use of IPR (i.e. actual situation of Ogura, where INRA grants non-exclusive licenses). For reasons of simplicity we focus on the interface between seed companies and farmers and hence distinguish two groups:

- Producer: INRA, seed companies and distributors
- Consumers: farmers, downstream industry and end-consumers

Because we cannot rely on observed data we must resort to modelling, which is described in the Appendix III. Essentially, using observed data, we derive a demand curve for Ogura technology, which describes at what seed price how many farmers decide to switch. That in return allows us to analyse how a rational producer would maximise its revenues.

The results presented hereafter of this single case study cannot be generalised as the optimal IPR use in agriculture depends on the technology itself as well as on local market dynamics.

5.1 Exclusive use for Ogura would lower uptake from 80% to 60%

Exclusive use of the innovation will grant more market power for the producer. But this greater market power does not mean unconstrained pricing power. If the producer prices the seed too high, adoption will be small and revenues will suffer whereas when it prices the seed to low, adoption will be high but margins will suffer. It turns out, as shown in Exhibit 13, that the optimal price for the producer will be € 11/kg higher than under non-exclusive patents, i.e. a € 24/kg premium on open-pollinated seed versus the actual € 13/kg premium.

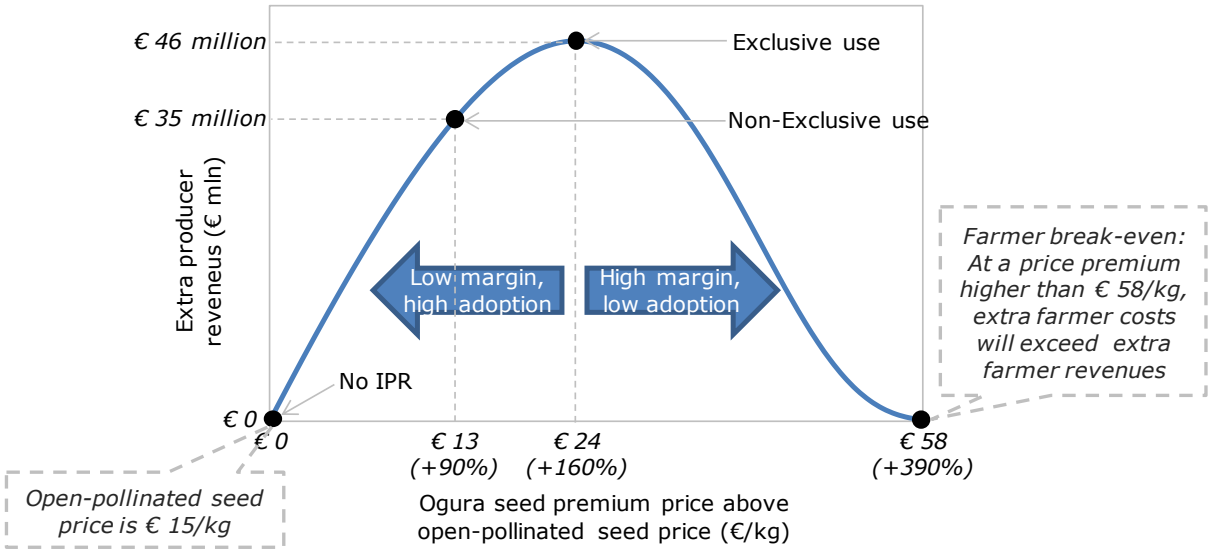

Exhibit 13: *Optimal Ogura seed pricing for maximum producer revenues*

Based on historical adoption data and using 2012 crop prices, the model shows that the percentage of farmers that adopt Ogura at this higher price decrease from 80%[46] to 60%; the higher seed price lowers the earnings per hectare such that 20% of the farmers deem them insufficient to switch. Relative to the actual premium of € 13/kg, producer revenues will go up 31% from € 35 million to € 46 million in 2012.

Although Exhibit 13 illustrates the increased market power coming from more IPR protection, it also shows that the pricing power of the producer is not unlimited. Whereas it is often assumed that patent holders are de-facto monopolists, the reality is that their market power is constrained by the presence of alternatives and the heterogeneity of individual farmer preferences.

In other words, it is the quality of the product in comparison with market alternatives and the heterogeneity of farmer appreciation of the technology that determine producer revenues and not just the strength of its IPR.

5.2 Exclusive use increases innovators' incentive and lowers current welfare

The 20% lower Ogura uptake causes the total economic benefits for society, or social welfare, to decrease by € 46 million (or 29%), in 2012. The consumer benefits will decrease by € 57 million (or 46%) whereas the producer benefit will increase with € 11 million (or 31%). A detailed explanation of these results is presented in Appendix III.3.

The larger producer benefit for the innovator acts as a larger incentive for the private sector to invest in R&D than under non-exclusive use of patents and thus increases the probability of innovations happening. This is particularly relevant as the private sector has overtaken the role from the public sector as largest investor in ag innovation. For example, since 2000 the private sector accounts for 80% of total R&D Oilseed Rape R&D.

Other research, summarised in Appendix III.4, has shown similar results for producer-consumer benefits once an innovation is made available to the market.

5.3 Non-Exclusive use seems appropriately balancing present and future benefits

The results presented in Section 5.2 enable a more in-depth exploration of the trade-off outlined in the research objective in Section 1.4. Exhibit 14 shows the consumer benefits (which accrue to farmers, processors and end-consumers) once the innovation is commercially available versus the producer benefit, which is used as proxy for the incentive to innovate. This seems a reasonable proxy as the variables that drive the ex-post producer benefits move in the same direction as the ex-ante incentive. In other words, when a producer would have perfect foresight of market conditions (e.g. crop prices, farmer willingness to adopt), its expected returns would largely influence its incentive.

Going to the left in Exhibit 14 from the actual case of non-exclusive licensing to the no IPR case shows that consumer benefit would increase with € 51 million (+41%), however at the cost of € 35 million producer profit and thus the elimination of the innovation incentive. The total social (i.e. consumer and producer) benefit would increase modestly with € 16 million (+10%). Going to the right to the exclusive patent case decreases consumer benefit with € 57 million (-46%) while it somewhat increases the producer benefit by € 11 million (+31%). The total social benefit would decrease by € 46 million (-29%).

The absence of IPR would lead to a modest increase of social consumer benefit at the very considerable cost of eliminating the innovation incentive and thus the probability of improved products becoming available in the future. Exclusive use of patents on the other hand would, in this case, modestly increase the innovation incentive at a substantial social cost.

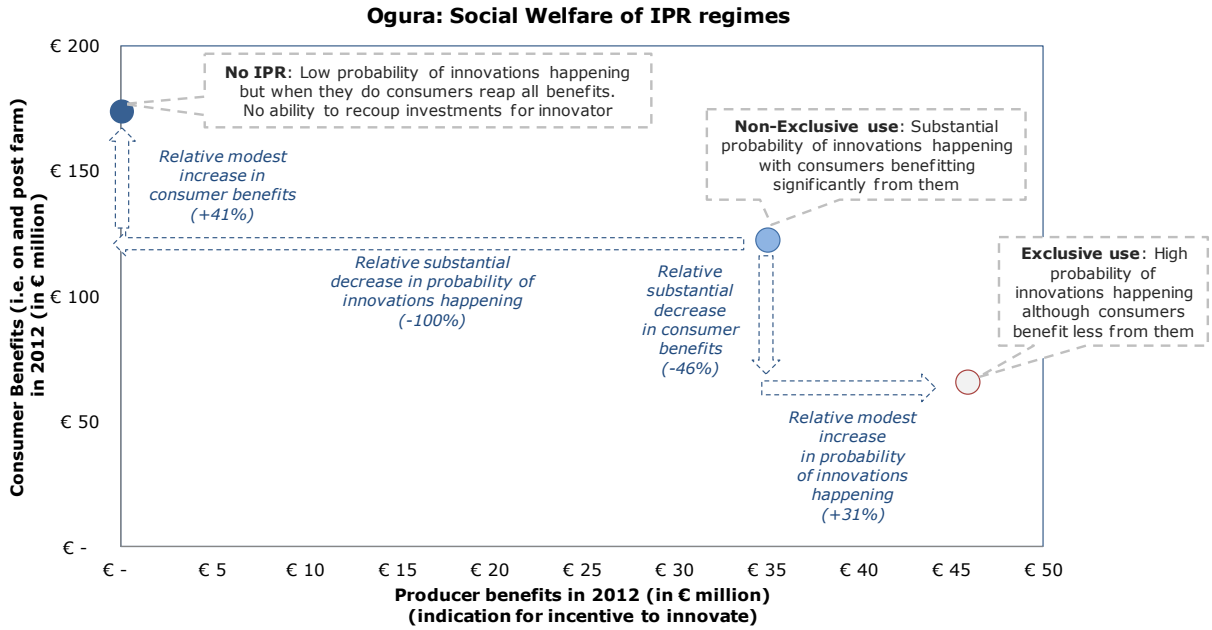

Exhibit 14: *Social welfare of Ogura under different IPR regimes in 2012. The consumer and producer benefits for these regimes are respectively: No IPR (€ 174 million, € 0), Non-Exclusive use (€ 123 m, € 35 m) and Exclusive use of patents (€ 66 m, € 46 m)*

In other words, the absence of IPR would increase the probability of missing innovation substantially, while exclusive use provide some increase to innovation incentive with a relative considerable cost for the consumer. Thus it seems that the non-exclusive use of patents has struck an appropriate balance between the current and future benefits. It is important to note that one cannot generalise based on the results of a single case study and the validity of the applied heuristic logic depends on many factors, prime among which the dependence of the incentive to innovate on the expected profits[47] and expectations about market prices for the crop. Therefore, the optimal IPR use in agriculture depends on the technology itself as well as on market circumstances.

6. Other socio-economic effects of Ogura

Section 4 highlighted the Ogura benefits for the farmers, seed companies and technology provider. However, the effects are not limited to economic costs and benefits. This section summarises the effects on resource efficiency and the employment effects of extra farm income.

6.1 Ogura reduces carbon footprint with 66 kg per ton of Oilseed Rape

According to other research on OSR production, water and energy use during drying and storage depend on the size of production, while other energy, fertilizer and pesticides use depend on the hectares of land used. As presented in Section 3, Ogura leads to 8% higher yields on average for OSR production. Therefore, producing an extra 330,000 tons OSR implies higher resource efficiency (see Table 1).

	Diesel	Fertilizer	Pesticide
Savings per tonne OSR	1.8 l	7 kg	0.07 kg
Total savings in 2012 (related to an extra 320,000 tonnes OSR)	7.9 million l	28 million kg	0.3 million kg

Table 2: *Estimated resource efficiency for OSR production related to Ogura in 2012*

When combined, the savings during the OSR production translate into a 66 kg carbon reduction per tonne[48] and almost 300,000 tonne CO_2-emissions in total, which is almost as much as the annual emissions of 150,000 cars.[49] With the 2008-2013 average market price of € 10 for a tonne of CO_2 emission this is equivalent to € 3 million. The broader environmental effects of Ogura are currently under examination by INRA.[50]

6.2 Annual € 123 million extra farm benefits results into almost 1,200 jobs

From 2000 - 2014, farmers earned € 631 million extra income due to higher yields from hybrid Oilseed Rape. The re-spending of the extra incomes on goods and services (i.e. induced economic effects) supports jobs elsewhere in the economy. The majority of these supported jobs can be found in the various service sectors, as indicated in Exhibit 15. Especially since 2010, the number of job supported by these induced effects increased significantly to almost 1,200 jobs in 2012 and are associated with € 123 million extra farm benefits in 2012 (see Table 6 in Appendix II.3).

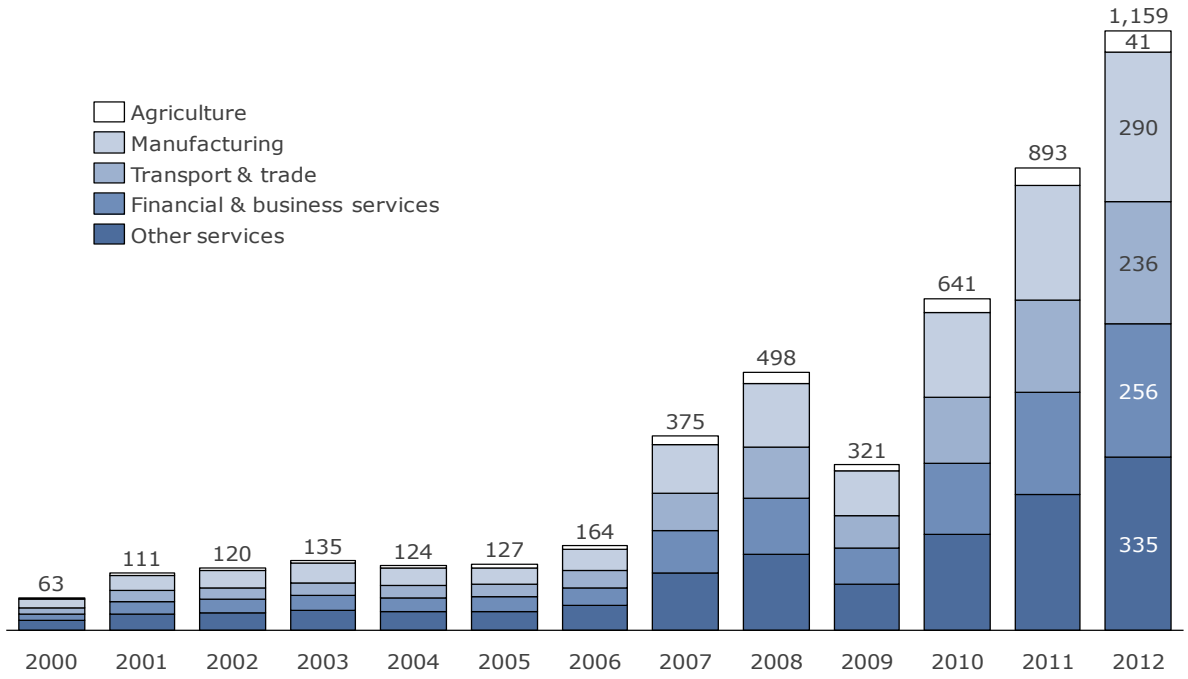

Exhibit 15: *Jobs related to re-spent of extra farm income (induced effects) 2000-2012*[51]

7. Recommendations

This report shows the trade-off between current and future benefits of IPR for ag innovation. In order to further validate the findings presented we recommend to:

- Apply the framework for other crops and markets in order to verify whether the conclusions on the effect of IPR strength on social welfare can be generalised;
- Investigate in greater depth the dependence of the innovation incentive on IPR regimes. In this report we have used the ex-post producer benefits as a proxy for the incentive to invest in (the next round of) innovation. By analysing trends of IPR strength and ag innovation using larger data sets this can be substantiated more.

Appendix I: Framework

I.1 Literature review social welfare of IPR use for ag innovation

The use of IPR for agricultural innovation and its effects on social welfare is discussed in several research papers. Many papers discuss the ex-post benefits and surplus division once the technology is in place, but also underline the importance of the ex-ante incentive for innovation.

Within the economic literature, IPRs are defined as economic institutions designed to address existing market failures that disincentivise R&D investment.[52] IPRs are meant to promote R&D investment and introduction of successful innovations by rewarding innovators with (temporary) market power on these products. In this way, innovators are better able to recoup their R&D investment.

An optimal IPR regime is a balance between innovation incentives and societal benefits. Therefore, IPR regimes must both encourage incentives for innovators and minimise the economic losses related to the market power of innovators (i.e. consumers losses as a result from high prices that exceed the market equilibrium, and the associated deadweight losses).[53]

IPRs are pull mechanisms that encourage the incentive to innovate through more stable, larger or efficient markets by increasing the expected innovator benefits.[54] For policy makers, pull mechanisms such as IPRs are attractive instruments because they do not request any ex-ante funding commitments, in contrast with push mechanisms such as research grants, tax reductions, etc. On the other hand, IPR regimes do require investments in effective enforcement and legislation.[55]

In short, the social welfare of agricultural innovation depends on the incentive to innovate (ex-ante) and the size of benefits during commercialisation (ex-post). The maximum welfare is obtained when maximising:

The number of successful innovations incentivised
x
The size of (consumer) benefits during product commercialisation

I.2 Definition 'size of benefits during commercialisation'

In this study we define the 'size of benefits' as the total net benefit created by Ogura in the entire value chain, consisting of the following actors: technology provider, seed company, distributor and farmer. Although in this research we allocate all benefits at the end of the chain to the farmer, in reality part of these benefits will leak away to downstream actors because wide adoption of Ogura will increase yields and thus lower OSR market prices. In general, yield-increasing technologies have a decreasing effect on crop prices[56], and would lead to benefits of downstream industry (food, feed, energy production) and end-consumers. This effect is quantified in a Bt soy study, where the total benefit remains the same, but the farmer share is divided with industry and end-consumers.[57]

Farmer benefits are divided into hurdle profit and surplus. Surplus is what farmers ex-ante perceive as benefit, while the total benefit is the actual total income created by the new technology (see also Appendix II and III). While the innovator and seed company surplus is closely related to their gross margin, the consumer surplus is the difference between what consumers pay and their ex-ante willingness to pay.[58] For example, while a farmer would increase earnings at a seed price premium of € 20 per kg, he may only switch when the premium is € 10. This means that at a price premium of € 10 his economic surplus (perceived benefit) is zero, although the adoption will increase his profits. In this report we have looked at the total benefit, i.e. the sum of hurdle profit and surplus.

The strength of an IPR regime affects the level of competition and the size of the benefits.[59] A strict IPR regime will lower competition, increase prices, lower uptake and therefore decrease the size of the benefits. The size of benefits under patent use can also vary depending on its effects on the Freedom to Operate (FTO).[60] The number of patents needed to commercialise a product and the number of patent holders have a large effect on the FTO as these factors increase the hurdle for a technology provider or seed producer to develop technologies and products in terms of access and costs.

I.3 Definition 'incentive to innovate'

The economic incentive for an innovator depends on the size of the expected benefits and the difficulties and risks to obtain these benefits. Protection through IPR gives the innovator more market power, which enables him to recoup investments and earn profits for shareholders and new innovations. Stronger IPR give innovators the ability to gain a larger benefit of their new technologies, which encourages R&D investment.[61] These incentives explain to a large extent the behaviour of the private sector according to the neo-classical economic theory, but not or to a limited extent public sector behaviour regarding R&D investments.

Appendix II: Economic benefits and benefits division of Ogura

II.1 Revenues, costs and benefits of technology provider INRA

Revenues

The INRA Ogura license revenues are estimated based on:

- Royalties of 1991 patents (4% royalty over licensee revenues, i.e. seed companies) and 1996 patents (1% royalty)
- Market share information of the French seed association (UFS) and seed price information of AMIS Global database of Phillips McDougall

The revenues originating from the French market are summarised in Table 3. Until 2011, France represented almost 30% of global revenues.

Year	Cumulative royalty rate	Total Ogura license revenues in France (in € million)
2000	5%	€ 0.3
2001	5%	€ 0.5
2002	5%	€ 0.5
2003	5%	€ 0.6
2004	5%	€ 0.6
2005	5%	€ 0.7
2006	5%	€ 0.7
2007	5%	€ 1.2
2008	5%	€ 1.7
2009	5%	€ 1.8
2010	5%	€ 2.3
2011	5%	€ 3.5
2012	1%	€ 0.7
2013 (est)	1%	€ 0.7
2014 (est)	1%	€ 0.7
2015 (est)	1%	€ 0.7
2016 (est)	1%	€ 0.7
Total		**€ 17.8**

Table 3: *INRA Ogura license revenues and royalty rate in France*

Costs

An estimate of INRA's Ogura investments are derived from the R&D breakdown of hybrid seeds listed in Table 4 and INRA-transfert documents and interviews, the license management body of INRA. According to INRA-transfert, Ogura was licensed halfway the proof of concept phase. Therefore, 100% of the 'discovery' costs and 50% of the 'proof of concept' phase are allocated to INRA. Together, the total INRA research investments sum up to € 5 million. As the scope of the study is France, we have used OSR production in France as share of total European production to allocate costs to the French market (€ 1.4 million based on 26% European OSR share).

R&D phases hybrid seed	Investments (€ million)		
	Minimum	**Maximum**	**Middle**
Discovery: Basic research, idea identification	€ 1	€ 4	€ 3
Phase I: Proof of Concept	€ 4	€ 7	€ 6
Phase II: Early development	€ 7	€ 11	€ 9
Phase III: Advance development	€ 11	€ 22	€ 17
Phase IV: Pre-launch	€ 0.7 per variety		

Table 4*: R&D phases of hybrid seed*[62]

II.2 Revenues, costs and benefits of seed companies

Revenues

The seed company benefits represent the extra revenues of selling Ogura hybrids in France. These extra benefits are equal to the Ogura price premium multiplied with the quantity Ogura hybrids sold *minus* the Ogura royalty payments (see Appendix II.2). It is assumed that the production costs of Ogura and open-pollinated seeds are similar. The French seed market data is based on UFS and AMIS global information. The seed

company benefits are presented in Table 5 and the Ogura market share since introduction in Exhibit 2.

Year	Extra seed company Ogura revenues (€ million)	Royalty Costs (€ million)	Seed company net benefits (€ million)
2000	€ 1.9	€ 0.3	€ 1.5
2001	€ 2.7	€ 0.5	€ 2.3
2002	€ 2.8	€ 0.5	€ 2.4
2003	€ 3.2	€ 0.6	€ 2.7
2004	€ 3.5	€ 0.6	€ 2.9
2005	€ 3.7	€ 0.7	€ 3.1
2006	€ 4.1	€ 0.7	€ 3.4
2007	€ 7.6	€ 1.2	€ 6.4
2008	€ 10.8	€ 1.7	€ 9.1
2009	€ 13.4	€ 1.8	€ 11.6
2010	€ 17.0	€ 2.3	€ 14.7
2011	€ 29.9	€ 3.5	€ 26.4
2012	€ 26.6	€ 0.7	€ 25.9
2013 (est)	€ 26.6	€ 0.7	€ 25.9
2014 (est)	€ 26.6	€ 0.7	€ 25.9
2015 (est)	€ 26.6	€ 0.7	€ 25.9
2016 (est)	€ 26.6	€ 0.7	€ 25.9
Total	**€ 233.9**	**€ 17.8**	**€ 216.0**

Table 5: *Seed company net benefits of Ogura in France 2000-2016*

Costs

The upfront Ogura development costs of the seed company can be separated into European and country specific investments. Phase I (50% for seed company), Phase II and Phase III as listed in Table 3 are European investments, while Phase IV are country specific investments. According to Monsanto UK, an estimated number of five seed companies have taken full development costs at the European level. Furthermore, 'AMIS Global' reports that 23 Ogura varieties have been introduced in the French market since 2000. Therefore, the development costs for France can be estimated as follows:

- Ogura development costs in Europe (Phase I - III): 5 firms x € 29 = € 144 million
- Ogura development costs in France (Phase I - III), allocated based on French OSR production in Europe: 26% x € 144 million = € 37 million
- Phase IV: € 0.7 million x 23 varieties = € 17 million
- Total development costs in France (phase I - IV): € 17 million + € 37 million = € 54 million

II.3 Revenues and benefits of farmers

The farmer benefits in the study represent the extra benefits of farmers that have adopted Ogura. In other words, the extra yield multiplied with the OSR price *minus* the extra seed costs. The production data, Ogura market share and seed costs information are based on Eurostat, Prolea, UFS and AMIS Global seed market data and presented in Table 6.[63]

Year	Extra revenues Ogura farmers (€ million)	Extra seed costs (€ million)	Net farmer benefits (€ million)
2000	€ 7	€ 2	€ 5
2001	€ 12	€ 4	€ 9
2002	€ 13	€ 4	€ 10
2003	€ 15	€ 4	€ 11
2004	€ 15	€ 5	€ 11
2005	€ 16	€ 5	€ 11
2006	€ 21	€ 5	€ 15
2007	€ 46	€ 10	€ 36
2008	€ 63	€ 14	€ 49
2009	€ 48	€ 17	€ 31
2010	€ 87	€ 22	€ 65
2011	€ 133	€ 39	€ 94
2012	€ 158	€ 35	€ 123
2013	€ 124	€ 35	€ 90
2014	€ 105	€ 35	€ 70
2015 (est)	€ 105	€ 35	€ 70
2016 (est)	€ 105	€ 35	€ 70
Total	**€ 1,075**	**€ 304**	**€ 771**

Table 6: *Farmer costs and revenues during Ogura patent life (2000-2016)*

Appendix III: Analysis of on and post benefits in OSR value chain

III.1 A demand curve for rapeseed

Exhibit 16 summarises the theory regarding fuel crop market dynamics. There is probably no other crop than rapeseed that is so intensively used for fuel production, especially in the EU (i.e. two-third of rape oil for biodiesel production). The first graph shows that OSR crop demand is the combination of fuel and food demand. Left from point (P', Q') there is no fuel demand, which could be the results of food shortages or low fuel prices making biofuel production less attractive.

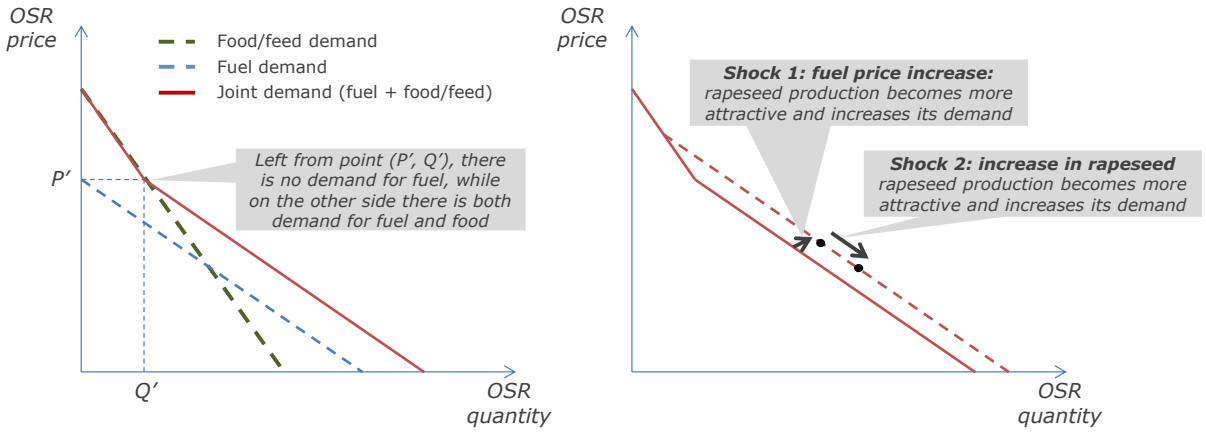

Exhibit 16: *Theory of rapeseed market dynamics*[64]

The second graph in Exhibit 16 shows two possible shocks in the rapeseed market. *Shock 1* shows the effect of an increase in the fuel price. This will increase the

attractiveness of rapeseed production and therefore the demand curve shift to the right. *Shock 2* is an increase in rapeseed production (e.g. because of new technology or extra land in production), which will have a lowering effect on the crop price. The size of the price decrease depends on the slope of the demand curve.

In our research, we analyse the effects of the Ogura-related supply shock (similar to *shock 2*). Since the introduction of Ogura seeds, there has been rape demand for fuel (see Exhibit 19), so therefore we focus only on the construction of demand curve for fuel, right from point (P', Q') in Exhibit 16. Consequently, a rapeseed demand curve can indicate the effect of a supply shock on prices and consequently the shift from on- to post-farm benefits.

In principle, the rape demand for fuel is almost perfectly elastic resulting in a vertical demand curve and mainly driven by the fuel price and biofuel quota (see also Exhibit 19).[65] However, as also explained in Section 4.3, crushing of rapeseed into rape oil for fuel demand produces also the by-product rape meal with more inelastic demand. Therefore, the demand curve is the weighted average of fuel and meal demand, see Exhibit 17. The slope of the meal demand is based on the historic info of rape meal prices and its supply (see Exhibit 20).

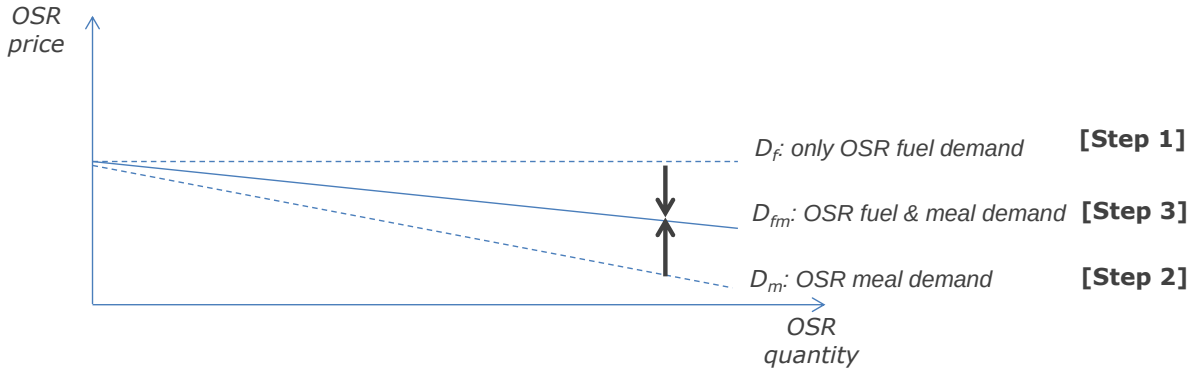

Exhibit 17: *Construction of rapeseed demand curve based on weighted average of rapeseed fuel and meal demand*

In the remaining part of this section, we explain how the demand curve was constructed for the year 2012 (see Exhibit 18) and a similar procedure is used for all the other years during 2000-2014. As a starting point, the demand curve for fuel is drafted as a vertical line (perfectly elastic) through the actual rapeseed quantity and price of 2012.
Secondly, we integrate the meal demand into the rapeseed demand curve:

- Extra EU rape meal increases the price gap between soy meal and rape meal (i.e. soy meal price premium): from 2000-2014, every extra million ton rapeseed resulted on average in € 15.6 per ton price premium. We interpret this as the lowering effect on the rape meal price because of extra rape meal production.
- A lower rape meal price decreases the benefits of the crusher.
- The lower crusher benefits are balanced out by lower rapeseed prices (see also explanation III.2)

This procedure translates an expected decrease of rape meal prices into a decrease of the rapeseed price in 2012 and thus the demand curve we set out to construct.

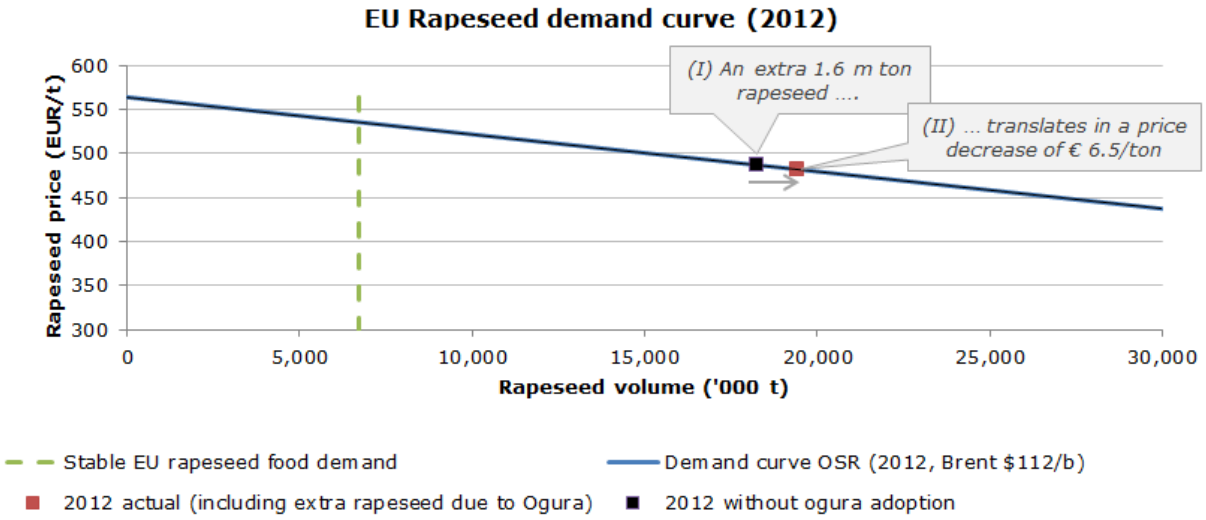

Exhibit 18: *EU rapeseed demand curve in 2012*

Using the rapeseed demand curve in 2012, we estimate that an additional 1.6m ton in the EU (i.e. supply shock related to Ogura seed adoption) translates into a price decrease of € 6.5/ton. Accordingly, we can use this price decrease in the EU to estimate the benefits that shift from on- to post-farm in France. In 2012, French rapeseed farmers produced 5.29 m tons, which is sold for € 6.5/t lower price due to Ogura. This shifts 5.29 m ton x € 6.5/t = € 34.3 m from French farmers (adopting and non-adopting) to post-farm (see also table 8).

Similarly, we estimated the EU demand curve and supply shocks for each individual year and its consequence for post-farm benefits in France. Appendix III.4 summarizes the key results using these demand curves.

Theoretically, an increase in biofuel volumes could also decrease fuel prices and consequently prices of biofuel, rape oil and rapeseed), but is unlikely due to the relatively low extra biodiesel volume related to Ogura vs the total fuel market.[66]

III.2 Balancing out price changes in the biofuel chain

According to Schmidhuber (2007),[67] prices in the biofuel chain are highly related to oil prices "*once oil prices have crossed a certain threshold making biofuels competitive*". Based on this relationship, prices in the biofuel chain seem to balance out competitive advantages vs oil after each change "*until the competitiveness of biofuels with fossil fuels equalises*". Hertel and Beckman (2011)[68] seem to underline these relationships, but also emphasise that evidence could be improved by larger historical datasets.[69] Building on this initial evidence, we assume that lower crusher profits is balanced out by lower rapeseed prices (i.e. equalizing lower rapeseed costs for the crusher with lower benefits from rape meal).

III.3 Market relations in the rapeseed value chain

Here, we summarize key relations in the OSR chain that also have been used in drafting the demand curve. The left-hand side of Exhibit 19 shows that the extra rape oil production in the EU since 2003 is completely used for fuel and is largely driven by the fuel price. The correlation between fuel price and rape oil for fuel production one year later is high (0.87). This is a strong indication that higher fuel prices significantly increase the incentive to produce rapeseed and rape oil.

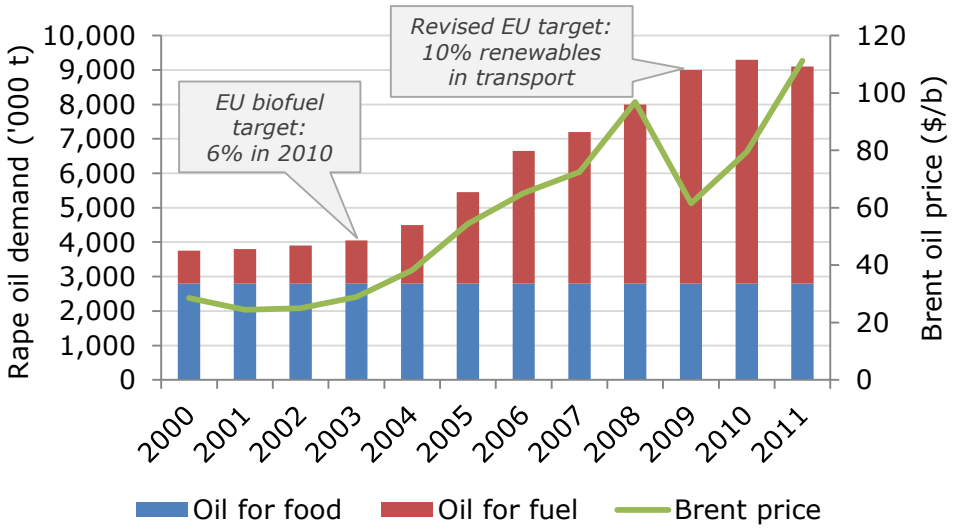

Exhibit 19: *Rape oil consumption vs Brent oil price (i.e. correlation between Brent oil price and EU rape oil production one year later is high: 0.87)*

Rapeseed is also used for producing rape meals, a by-product during the crushing process to produce oil. Rape and soy meal represent almost the full market of protein-rich feed for livestock in the EU and are partly substitutes for several feed markets.[70]

The left-hand side of Exhibit 20 shows that the price difference between soy and rape meals (i.e. soy meal premium) increased in line with the increased rape meal production in the EU. Based on the comparison between this premium and the additional EU rape meal on the market, we can derive the following relation: every extra million ton rape meal increases the premium with € 15.6 per ton (i.e. regression coefficient in Exhibit 18, see right-hand side), with a high correlation of 0.82.

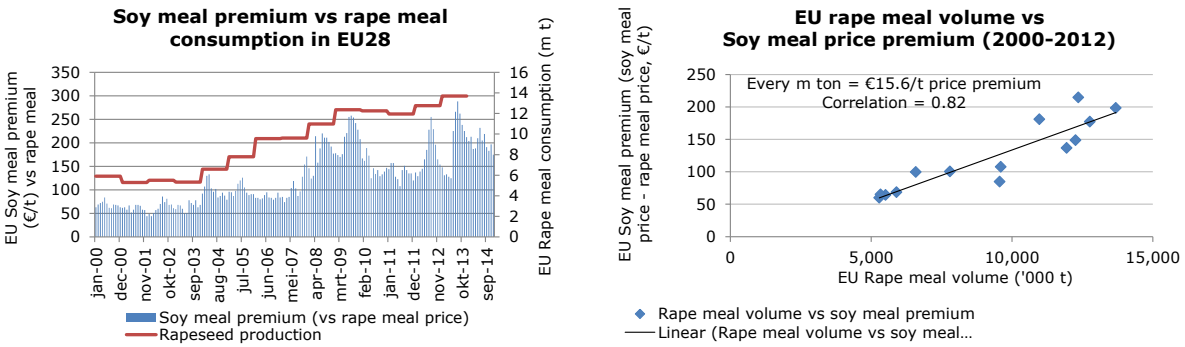

Exhibit 20: *Soy meal premium (i.e. price difference soy and rape meal) in comparison to rape meal consumption in EU 28 (left), and EU rape meal volume relation with soy meal price premium (right)*

III.4 Results estimated rapeseed price changes, on- and post-farm benefits

See below the estimated price changes due a 'supply shock' of rapeseed and its effects on and post-farm benefits.

Year	Ogura farmers yield benefit (€ million)	Price change (€/ton)	Production Ogura farmers (million tons)	Loss due to price (€ million)	HR on-farm benefit after price correction (€ million)
2000	5	0.3	0.5	0.2	5
2001	9	0.4	0.8	0.3	8
2002	10	0.3	0.8	0.3	9
2003	11	0.4	0.9	0.4	11
2004	11	0.4	1.0	0.4	10
2005	11	0.5	1.1	0.6	11
2006	15	0.9	1.2	1.0	14
2007	36	1.5	2.0	3.0	33
2008	49	1.5	2.5	3.7	46
2009	31	3.0	2.5	7.5	23
2010	65	4.6	3.3	15.1	50
2011	94	6.0	4.0	24.0	70
2012	123	6.5	4.4	28.8	94
2013	90	6.3	4.4	27.9	62
2014	70	6.5	4.4	27.9	42
Total	**631**	**n/a**	**34**	**141**	**489**

Table 7: *Effects of yield and price change on Ogura farmers in France (2000-2014)*

	Price change (€/ton)	Production other farmers (million ton)	Loss other farmers (€ million)	Total post-farm of rapeseed farmers (€ million)
2000	0.3	4.5	1.6	1.7
2001	0.4	4.2	1.5	1.8
2002	0.3	4.2	1.4	1.7
2003	0.4	4.1	1.8	2.2
2004	0.4	4.0	1.6	2.0
2005	0.5	4.0	2.1	2.6
2006	0.9	3.9	3.4	4.4
2007	1.5	3.1	4.8	7.8
2008	1.5	2.7	4.0	7.7
2009	3.0	2.6	7.9	15.4
2010	4.6	1.9	9.0	24.1
2011	6.0	1.2	7.4	31.5
2012	6.5	0.8	5.5	34.3
2013	6.3	0.8	5.3	33.2
2014	6.3	0.8	5.3	33.2
Total	**n/a**	**43**	**62**	**203**

Table 8: *Effects of yield and price change on other rapeseed farmers and total effects on rapeseed farmers in France (2000-2014)*

Appendix IV: Effects of IPR strength

IV.1 Definition producer and consumer

All actors in the value chain are grouped into two groups, 'Producer' and 'Consumers' in order to be able to compare other IPR regimes with the actual regime (i.e. non-exclusive use of patents). This also allows for better comparability with other research. The Producer includes all parties that have been involved in bringing the seed technology to the market: technology provider INRA, seed companies and distributor. The Consumers include all the parties that benefit from improved Oilseed Rape production: farmer, downstream industry and end-consumers.

IV.2 Drivers for Ogura uptake

The overview below gives a brief description of all drivers for Ogura uptake:

- Seed price: strict IPR regimes limit competition and increase prices, which lower uptake
- Crop price: a higher crop price increases earnings per hectare of farmers. Therefore, uptake of Ogura seed will have more impact on extra revenues when OSR prices are high;
- Heterogeneity of farmers: Dillen[71] demonstrated that for other ag innovations the benefit sharing is a direct reflection of the heterogeneity of farmers' technology valuation. Therefore, each farmer ex-ante perceives and values new technology differently and makes his own choice whether and when to adopt a new technology.
- Farmer economic benefit of new technology: the economic benefit describes the value for the farmer when adopting a new technology. The three main benefits are: yield increase, decrease of production costs and increase in crop value. Other benefits could be lower volatility in crop yields, lower environmental footprint, etc.

IV.3 Derivation of demand curve for Ogura seed

The essence of the economic model is the derivation of the demand curve for Ogura based on farmer economics. Each farmer makes an individual decision to adopt hybrids depending on the extra earnings per hectare. Extra earnings are driven by: changes of the crop price, yield increase of hybrids and higher seed price for hybrids. Market behaviour therefore is described as a lognormal probability distribution of switching decisions. The distribution indicates the percentage of farmers that will have switched for a particular earnings increase. Using this procedure, the demand for hybrid seed can be estimated and is converted from an exogenous into an endogenous variable, which incorporates crop price change, yield change of hybrids and seed price changes.

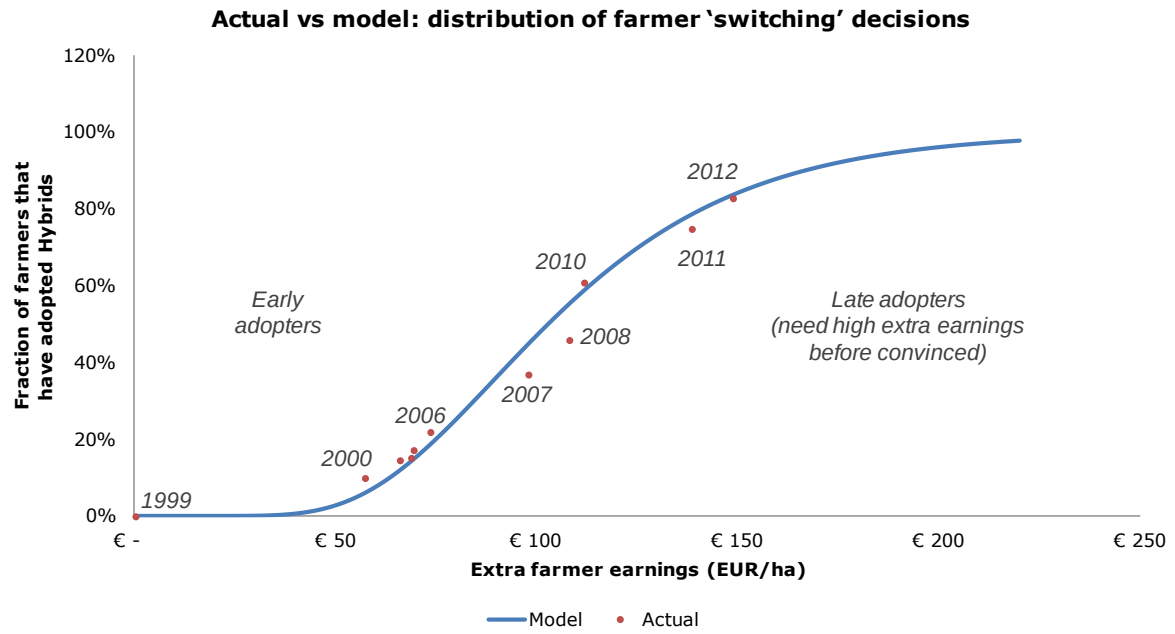

Exhibit 21: *Distribution of farmer 'switching' decisions*

The (cumulative) probability distribution in Exhibit 21 describes the switching decisions of farmers based on extra farm earnings related to Ogura. The growth in hybrid market share and farmer earnings translate into a probability distribution using a Least Squares fitting procedure. The estimated probability distribution reflects the switching decisions of each individual farmer.

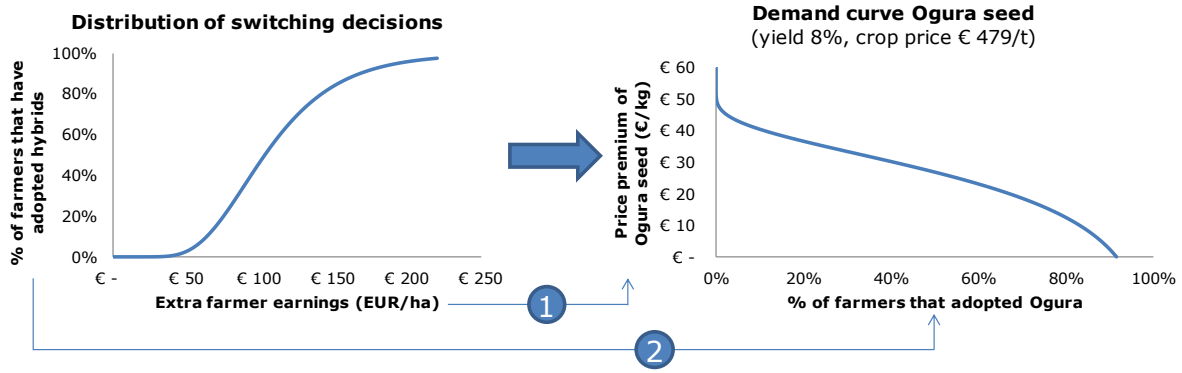

Exhibit 22: *Derivation of seed demand curve from distribution of switching decisions*

As presented in Exhibit 22, the demand curve for Ogura seed is derived from the probability distribution of market share and farmer earnings. The price for Ogura seed at which a farmer switches can be calculated for any given crop price and yield increase. By plotting these seed prices against the fraction of farmers that have adopted hybrids one obtains the demand curve which indicates the fraction of farmers that have adopted Ogura at each seed price premium.

IV.4 Breakdown of Ogura results for No IPR, Exclusive and Non-Exclusive use

Exhibit 23 shows the price equilibrium of exclusive use of patents versus the actual situation of non-exclusive use for Ogura. Under exclusive use, the producer has more freedom to set prices, but still has to consider the factors mentioned in Appendix III-2. From a producer perspective the revenue-maximising price depends on yield increase and crop price. For Ogura in 2012, the producer's optimum price premium is € 24/kg (see Exhibit 7). A lower price premium will lower margins and thereby decrease revenues (left-hand side), while a higher premium (right-hand side) would lower uptake levels to also decrease revenues. This optimum price caps the producer's surplus in 2012 at € 46 million in 2012 (see Exhibit 9).

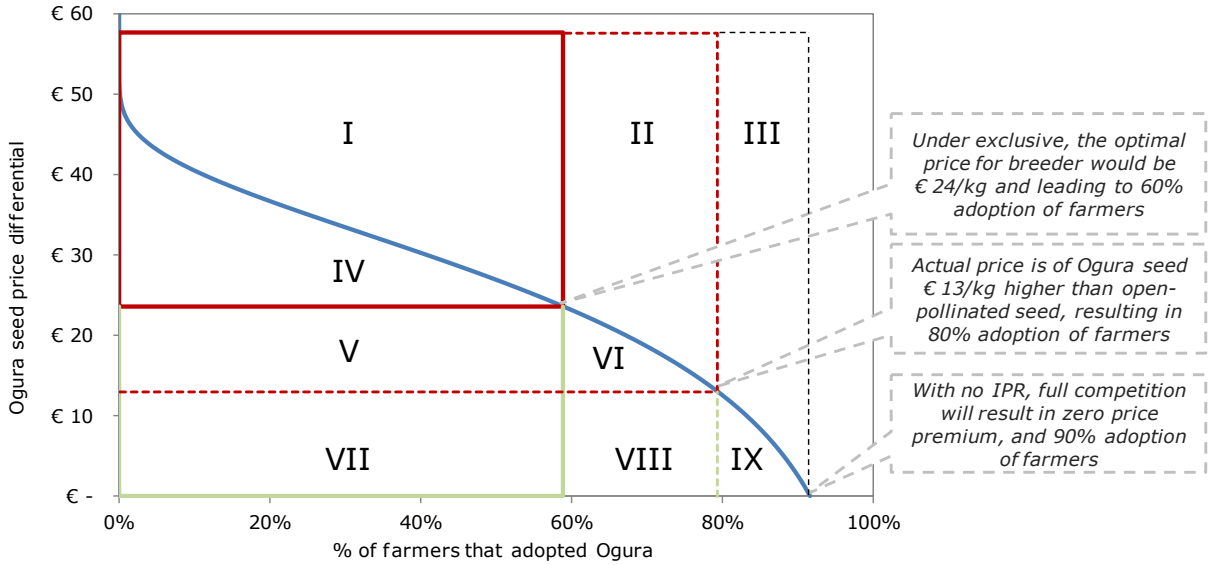

Exhibit 23: *Price equilibrium under No IPR, exclusive and non-exclusive use of patents in 2012*

The demand curve in Exhibit 23 shows that a price premium of € 24/kg corresponds with a 60% farmer uptake under exclusive use, € 13/kg premium (non-exclusive licensing) results in 80% uptake, and no premium (no IPR) in 90% uptake. Table 9 describes the outcome in terms of consumer and producer benefits as a result of the price premium and uptake. The producer surplus is described by the area between the x-axis, uptake level and the price premium. The consumer surplus represents the area below the demand curve and the price premium, while the hurdle profits is the area between the maximum price premium (€ 58/kg, break-even farmer) and the demand curve.

	No IPR	Non-exclusive use of patents	Exclusive use of patents
Consumer benefits	€ 174 million	€ 123 million	€ 66 million
Hurdle profits	I + II + III = € 94 million	I + II = € 78 million	I = € 46 million
Consumer surplus	IV + V + VI + VII + VIII + IX = € 80 million	IV + V + VI = € 45 million	IV = € 20 million
Producer benefits	-	VII + VIII = € 35 million	V + VII = € 46 million
Total benefits	**€ 174 million**	**€ 158 million**	**€ 112 million**

Table 9: *Consumer and producer benefits and related areas in demand curve (Exhibit 15) in 2012*

Exhibit 11 summarises the total benefits of Ogura during patent life under non-exclusive use (left-hand side, actual results) in comparison with exclusive use (right-hand side, model results). The producer benefit is similar to the producer surplus (i.e. gross margin of producer), while the consumer benefits can be broken down into consumer surplus and hurdle profits based on the equilibriums in Exhibit 15:

- Exclusive use: € 20 million consumer surplus, € 46 million hurdle profits (i.e. total consumer benefit of € 66 million)
- Non-exclusive use: € 45 million consumer surplus, € 78 million hurdle profits (i.e. total consumer benefit of € 123 million)

The total consumer benefit (i.e. including both hurdle profits and consumer surplus) under exclusive use is equal to 59% of total benefits (based on 2012 circumstances): € 66 million / € 112 million. This share can be compared with other studies:

- Benefits from BT cotton have been examined by several studies[72] and report a consumer benefit in the range of 51%-74%.
- Studies on herbicide resistant soybean[73] report a more divergent picture with total consumer benefit in the range 31-90%.

The consumer surplus (i.e. excluding hurdle profits) as share of total surplus is 31% under exclusive use, € 20 million / (€ 20 million + € 46 million), and can be compared among others with:

- Theoretical exercise of welfare effects under different IPR regimes (no IPR, PBR and strong patents) is executed by Perrin and Fulginiti.[74] The consumer surplus under strong patents ranges from 26-33% of total surplus.

Appendix V: Other socio-economic effects

V.1 Resource efficiency

The Ogura savings in terms of land use for OSR production are based on:[75]

- 1.6 million ha in 2012
- 3.1 t/ha open-pollinated seed yield and 3.35 t/ha Ogura seed
- 83% market share of Ogura seed in 2012

Therefore, the extra production using 1.6 million ha of land in France is:
(3.35 - 3.10 t/ha) x 1.6 million ha x 83% = 330,000 tonnes OSR.

Table 10 shows the resource efficiencies related to the extra OSR production.

OSR farm input (other than seeds)	Direct use	Total savings
Total fertilizer	293 kg/ha	31 million kg
N-fertiliser	*165 kg/ha*	*18 million kg*
P205 fertiliser	*59 kg/ha*	*6 million kg*
K20 fertiliser	*69 kg/ha*	*7 million kg*
Pesticides	2.8 kg/ha	0.3 million kg
Diesel (all activities and transport)	74 l/ha	7.9 million l
Electricity (storage, drying of OSR)	36.7 kWh/t	N/A (use per tonne)
Water	0.6 l/t OSR	N/A (use per tonne)

Table 10: *Resource efficiency per OSR farm input related to Ogura*[76]

V.2 Induced effects

The effects of re-spending farm income (i.e. induced effects) are based on:

- Extra farm income from 2000-2012 (see Table 5)
- Average spending pattern of French households on economic sectors originating from the French economic Input-Output table of GTAP 8[77]
- Average employment per 1 million revenues for each economic sector in France 2000 – 2012[78]

Appendix VI: References and notes

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EuropaBio position on germline genome editing

EuropaBio and its members strongly believe that genome editing will enable the development of many solutions to the grand challenges facing both people and planet. In medicine, genome editing offers the prospect of saving lives and tackling some of the most devastating genetic diseases.

It is crucial to note that all pre-clinical and human clinical testing by EuropaBio member companies, using genome editing for the treatment of genetically based diseases, is being done on non-heritable (somatic) cells. This means that it does not result in changes to the genes that a person passes on to their children. Clinical research with genome editing of human non-heritable (somatic) cells is currently seeking to develop treatments for HIV, leukaemia, haemophilia, Leber's congenital amaurosis 10, mucopolysaccharidosis, sickle cell disease and cystic fibrosis, amongst others.

Consistent with the principle of responsible stewardship of science, EuropaBio takes the position that it would be irresponsible at this time for anyone to proceed with clinical research for therapeutic use of genome editing of human germline (heritable) cells and embryos until (i) the consequences of such genome editing are more thoroughly studied and understood and (ii) a consensus on responsible and responsive global governance framework is reached. As it remains critically important that the current state of knowledge of genome editing is improved, such stay of clinical research with human germline genome editing should be limited in time and revised on a regular basis, along with the advancement of understanding of the scientific and technical environment, as well as the consensus on governance arrangements across the globe.

It is crucial that the global community, involving government, academia, industry, and society at large, gathers to discuss the technical, scientific, medical, legal, societal, and ethical issues associated with genome editing of human germline cells and embryos, with a view to establishing an international governance framework. It is also highly desirable that the international community of bioethicists steps up the research on the ethical dimensions of germline genome editing.

EuropaBio takes the view that once an established governance framework will allow clinical research in genome editing of human germline cells and embryos, such research should be carried out only with the intention to potentially provide therapies to serious and unmet patient needs. EuropaBio does not support the conduct of research in germline genome editing aimed at achieving human enhancement.

EuropaBio notes that the WHO convened an advisory committee to develop global standards for governance of human genome editing. This expert panel is currently working to set up a registry of research and development involving human genome editing. In this context, we would like to stress the importance of differentiating between genome editing of human somatic *versus* human germline cells. Remarkable progress has already been made in genome editing of human somatic (non-heritable) cells to treat diseases. All phases of clinical research involving genome editing of somatic cells are already registered in established databases, including the WHO International Clinical Trials Registry Platform (ICTRP), which the WHO plans to use for the new registry. Pre-clinical research on somatic genome editing should be excluded from any proposed registry.

EuropaBio's members adhere to a clear set of core ethical values and condemn, in the strongest terms, any actions that violate laws and regulations. We stand united with scientific and political leaders across the globe in our intention to contribute towards setting, following and enforcing guidelines and policies for the responsible research and application of genome editing of the human germline.

EuropaBio®

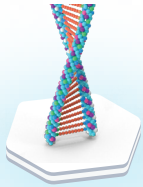
ADVANCED THERAPIES
TRANSFORMING MEDICINE

What are Advanced Therapy Medicinal Products?

Advanced therapies offer patients new hope against a range of devastating illnesses, such as inherited diseases, leukaemia, blindness, Parkinson's disease, epilepsy and many others.

Advanced Therapy Medicinal Products are a new generation of innovative medicines based on genes, cells or tissues. Advanced therapies have ground-breaking therapeutic potential, particularly in disease areas where treatment options are absent or inadequate. Excitingly, these therapies are starting to allow us to cure challenging conditions with a one-off treatment. As a result, they also have transformative implications for families, society and healthcare systems.

There are three types of advanced therapies:



Gene therapies

Cell therapies

Tissue-based therapies

Gene therapy alleviates the disease root cause or symptoms by replacing a malfunctioning gene or introducing a novel gene-based approach to help the patient return to good health. Gene therapies hold great potential for treating, preventing or curing a wide range of inherited conditions.

Cell therapy involves transforming cells in order to fight disease. Cells are adapted before being introduced into the patient's body where they target and treat diseased cells. The cells can be sourced from the patient's own body or from a healthy donor.

Tissue-based therapies seek to restore or replace damaged parts of the body through the combination of cells and active molecules. This aims to normalise the damaged cells' structure as much as possible. Such therapies may allow a tissue or organ to develop and grow inside the patient.

Where standard medical and surgical practice have not proved effective in curing or treating genetic diseases, advanced therapies emerge as a promising option for a potentially lifelong cure.

What advanced therapies are currently helping patients in the EU?

Here are some examples:

→ Patients with skin cancer and acute forms of blood cancer, such as leukaemia and lymphoma, are being treated by therapies which detect cancer cells and trigger the body's immune system to attack them.

→ Children with a rare inherited condition, causing their immune system to fail, are being treated by a therapy made from their own bone marrow.

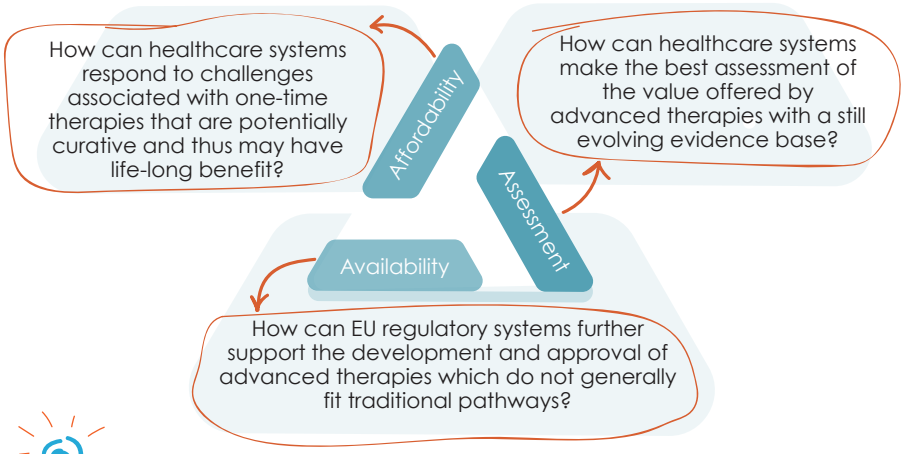
→ Patients who have been blinded through injury are having their sight restored by an innovative treatment using their own stem cells.

Since 2007 when the EU began to regulate advanced therapies, 14 advanced therapies have received marketing authorisation.

Advanced therapies that address the root cause of the disease with a one-time treatment can result in lower long-term costs for healthcare systems, compared to conventional treatments used for weeks, months, or even for life.

What are the challenges for the use of advanced therapies?

Advanced therapies represent a novel category of treatments and are often highly complex to develop and deliver. To fully maximise their potential, healthcare systems will need to adapt to ensure that patients across the EU can fully benefit. Advanced therapies pose new questions in three areas:



EuropaBio invites EU decision-makers to engage with us and our healthcare biotech members who are leading the field in advanced therapies.

We offer unparalleled knowledge and first-hand insight into the full range of issues relating to the pathway of innovative treatments from bench to bedside.

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