Genome Editing, R&D, and Heterogeneous Regulatory Regimes: Implications for Innovation and Agricultural Trade

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Genome editing, R&D, and heterogeneous regulatory regimes: Implications for innovation and agricultural trade

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Abstract: We provide an economic analysis comparing the Research and Development (R&D) cost of innovations based on genome-editing techniques with SDN1 and SDN2 alterations under two alternative regulatory regimes (GMO or conventional hybrid) using a discounted present value approach, including the cost of delays and for three case studies. The three cases rely on most recent cost information from experts opinion, summary data of R&D expenditure from dominant global biotechnology companies, and current research on grape genetics from INRAE in France. Despite the great heterogeneity of R&D cost across these three case studies, we find that GMO regulated R&D faces higher costs than under conventional-hybrid regulation. However, the range of relative costs of approvals between the two regulatory regimes is much smaller. The cost of GenEd R&D under GMO regulatory approval relative to that of being under conventional-hybrid regulation makes it 63% to 76% more expensive. This occurs despite the different commodities considered, their different industry organization and funding model of the R&D process. We further estimate the breakeven value of annual benefit from the innovation under the two regulatory regimes. A wide range is obtained across the three cases. Yet, the ratios of breakeven values under the alternative regulatory regimes (GMO v conventional-hybrid) exhibit a narrow range from 2.48 to 2.76 for the three cases. Required revenues to break even more than double under the GMO-like regulation. We draw some implications for the rate of innovation and international trade.

Keywords: GMO, present discounted value, genome editing, new plant breeding technique,

R&D, cost, approval, grapes, innovation, grapevine

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Genome editing, R&D, and heterogeneous regulatory regimes: Implications for innovation and agricultural trade

Introduction

We provide an economic analysis comparing the R&D costs of biotechnological innovations in agricultural crops and grapes using genome-editing techniques. Specifically, we focus on SDN1 and SDN2 genome-edited products, which can also be obtained using conventional hybrid breeding techniques, under two alternative regulatory regimes.[1] One regime treats GenEd innovations as conventional-hybrid breeding, and the alternative regime treats these genetic modifications as transgenic (GMO) innovations.

We first introduce an economic approach based on present value discounting to evaluate the cost differential between the two alternative regulatory environments and then presents three case studies documenting the relative high cost of considering GenEd innovations as GMO rather than conventional hybrids. The main implications are first that GMO-like regulation is much more costly, although absolute magnitudes vary between these three case-studies. However, the relative cost of the two regulatory regimes (their ratio) points to a narrower range of outcome, with the cost of innovations under the GMO regulation of GenEd innovations relative to its conventional-hybrid treatment, around 63% to 76% more expensive.

We estimate the breakeven annual benefits required under the two regulatory regimes for the three case studies. The results also show a wide range of values. The breakeven point of the R&D investment decision is also much higher under a GMO regime because of the long regulatory delays involved in GMO-like regulation. The most interesting finding is that the ratios of breakeven values exhibit a narrow range from 2.48 to 2.76, for the three cases. Under a GMO

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[1] We do not consider innovations using SDN3 genetic modifications with introduction of foreign DNA also achievable through genome editing techniques.

regulatory regime, the required annual revenue must be more than twice as large to break even on the R&D project.

Implications are drawn for the rate of innovation and prospects for international trade under asynchronous regulatory regimes based on these three cases. The analysis leverages most recent and new estimates of R&D cost in biotechnology (Lassoued et al., 2019; Agbioinvestor, 2022; and This and Beghin, 2023). The latter analyses go beyond the older evidence of Mc Dougall (2011), Bayer et al. (2010), Falck-Zepeda et al. (2012), Pray et al. (2005) and (2006), Kalaitzandonakes et al. (2007), and others. Qualitatively old and new literatures point to costly regulatory regimes and delays for GMOs. This and Beghin (2023) was initiated for the specific economic analysis presented here.

For the first two case-studies, the economic analysis relies on the most recent estimates of R&D cost for both GenEd and GMO products (Lassoued et al., 2019; and AgbioInvestor, 2022; the latter being an update of McDougall, 2011). For the grapevine case study, we rely on information obtained from INRAE in Montpellier, France, based on previous research projects developing new traits in recent years and summarized in This and Beghin (2023). INRAE in Montpellier specializes in grape genetics and is a privileged source of information on grapes genetics.

EU regulations for GMO approval are complex and lead to delays (Smart et al., 2017; see also appendix 2). They involved the overlap of EU-level and national-level processes. The EU process is summarized and reviewed in Bruetschy (2019) and EFSA (2021); the promise and advantages of GenEd in the EU context is provided by European Parliament Research Service (2022). Although the focus is on the EU context in this third case study, the US regulatory system has actually experienced increasing delays for GMO approvals surpassing EU delays

(Smart et al., 2017). The US delays were principally in the approval process rather than in the trial themselves, taking 1,146 days longer in the regulatory pipeline than the earlier (pre 1997) applications. Hence, lessons drawn here extend to the US environment and beyond.

Several studies measure biotech R&D cost in dollars terms (cost of different stages from research to commercialization post regulatory stage) and in duration time taken for every stage and or the approval time (Smart et al., 2017; Lassoued et al., 2019). In many studies, time is not converted into dollar equivalent. Therefore, the cost of delays is not fully factored in. The issue becomes then to decide how to convert time delays, especially the extended regulatory time, into dollars of present discounted value. In a straightforward way, the discounted value of expected revenues or savings from innovations is pushed back with delays and the R&D cost is front-loaded. Delays also induce some discounting of costs, presumably as they are spread over a longer period.

In this context, the pure delay of future revenues could be an upper bound on the cost of delay as some costs are also delayed. A countervailing caveat is that cost is incurred during approval periods and is still occurring and amplified by delays. In any case, the approach used here also implies having a good idea of futures revenues, which is difficult as we are considering potential innovations for which we do not know the market potential. To overcome this difficulty, we consider several levels of annual revenues. We also provide expected breakeven level of annual revenues in the three case studies analyzed for both regulatory regimes. Hence, we are able to estimate relative breakeven levels, and the amplification induced by a GMO regulatory regime for GenEd innovations.

Another issue is the overlap of stages in the R&D process. Not all studies address this issue. However, several studies come with a sequence of the steps, including their overlap to determine the total duration of the project. This is useful as the cost of each stage can be spread over the estimated time and with the overlap of the stage explicitly accounted for. Lassoued et al. (2019) do not describe the overlapping stages explicitly but provide a sequence of non-overlapping steps. The latter information can be used.

A further issue is the substantial variance in the recent cost estimates of developing a new or modified trait using biotechnology. Their underlying assumptions and commodities are different. The range goes from a few million dollars (grapevine case, values in Lassoued et al., 2019), to $115 million (AgBioInvestor 2022). The description of the innovation varies and sets the bar higher in the AgBioInvestor case with an approval process obtained in two countries to grow the crop and imports allowed in five geographical markets. The latter case illustrates the R&D process in a global/international context with production and exchange across borders. To reduce this variance, we also provide relative costs of the innovation process under the two alternative approval regimes (GMO, conventional-hybrid breeding). The range of relative cost decreases dramatically. Duration estimated by these studies show less substantial variation, but still requires accounting for the overlap issue noted above.

The foundations of our analysis of cost of delay of GenEd innovations are based on Van Eenennaam et al. (2021 and supplement), Wesseler et al. (2017), AgBioInvestor (2022), Lassoued et al. (2019), and information originating in various projects at INRAE Montpellier on grape genetic research presented in This and Beghin (2023).

We focus on GenEd innovations addressing climate change mitigation being regulated alternatively as conventional hybrid, versus being treated as transgenic (GMO). We start in a first case first with a simple approach with no overlap of stages in the R&D process and focus on a calibration using data generated by Lassoued et al. (2019) and the consensus values of cost and duration for a generic innovation (a new trait).

In a second case, we account for the overlap of stage using AgBioInvestor's estimates of duration and costs in GMO R&D which we adapt for GenEd. This second case focuses on actual cost of R&D and innovations by four dominant agro-chemical and biotech firms innovating in the commodity space for corn-maize, oilseeds (soybeans, canola), and cotton, but not grapes. These firms commercialize these innovated commodities beyond their borders for planting and other uses.

The third case study focuses on a new genome-edited trait in grapevine used for wine production in the European Union, and France in particular, using parameters on duration and costs which reflect the actual grape variety regulation in France and Europe, cost of innovation in public research institutions in France, and observed time to develop the science and get it approved. The types of innovations we have in mind include the avoidance of excessive sugar and alcohol, color loss, various biotic and abiotic stresses reducing yields, and which could be addressed by GenEd innovations to adapt to climate change (See This and Beghin, 2023 for more details and Appendix 1 in this manuscript).

This last case study assumes that grapevines can be edited without the insertion of foreign DNA (SDN1 and SDN2 only, excluding SDN3), a nascent methodology in research centers working on grapes (EUSAGE, 2023). EUSAGE lists eight such genetic manipulations reported worldwide for grapes. The development of a new trait in grapes is lengthy and its expected cost is not fully known. In addition, our case study considers the cost of the development of one edited variety from a well-known cultivar already grown such as 'Pinot,' 'Merlot' or 'Cabernet-Sauvignon.' We consider two subcases, one to develop a new variety, and a second one to develop a clone of an existing variety, considered as of the same variety. Some time and cost saving occur under the clone case, but qualitative results are essentially unchanged. The cost of breeding other varieties with the same constructs will be lower in the future, as initial tests and optimizations will already have been completed, reducing the time required for subsequent innovations.

In the next sections, we formalize the modelling approach, and then its application in the three case studies. In closing, we draw implications for innovations and international from these three case studies.

2. Modeling Approach

The approach includes two main elements: adoption of the innovation by market participants, and the time and extent of market penetration, which may vary among producers and consumers. Under GMO regulations, this penetration might be slower than under GenEd regulation, with reluctance of market participants and higher cost and longer delays. Second, these innovations take time and resources. The approach accounts for proper valuation of the streams of costs and future revenues, and delays though discounting of these futures streams.

We first address the adoption step. As in Van Eenennaam et al. (2021a), we start from a logistic model of diffusion of the GEnEd innovation into the considered market:

$$P_t = \frac{k}{(1+e^{-(a+bt)})}, \ (1)$$

with P_t being the proportion of the industry (producers) adopting the GenEd innovation at time t, and with parameters a being the initial adoption indicator, and b characterizing the speed of diffusion over time and convergence to k, the long-term proportion of the industry adopting the innovation. Parameter a reflects where the market starts when the innovation has just been approved and commercialization is initiated. Parameter k is the diffusion parameter ($k \in (0,1)$). Time t varies between 0 and T. The time period is assumed to be 30 years in the first two case-studies, and 35 years in the last case-study reflecting the longer duration of grapevine research. Regulatory approval is assumed to be achieved at time N (N_{GenEd}, N_{GMO}) with $N<T$. Time T is sufficiently distant in time for P to reach k and generate gains from the full-potential adoption ($P=k$) of the innovation for many years.[2]

Next, we outline the sequence of costs, benefits, and delays that occur over time. Define C_t as the annual cost at time t of the various stages of the innovation process as summarized in Table 1. The cost varies over time, depending on the various stages of the R&D process. Let us define pecuniary benefits (i.e., revenues) at time t from the innovation as B_t. Benefits are zero until the approval of the innovation is complete; then they grow with adoption and diffusion and reach a steady state maximum value after full adoption when $P_t=k$. The streams of costs and benefits vary between the two regulatory regimes because some steps have different costs and because of the delays under the GMO regime. When adoption has converged to its steady state, the annual benefit is assumed identical under the two regulatory regimes.

The saving concept developed here, captured by *Savings* in equation (4) accounts for the differences in R&D costs, costs for approval and market commercialization, as well as the cost of delays that are avoided if the GenEd innovation is made under the GenEd regulation rather than under a GMO regulation. The differences are expressed in the Present Discounted Value, PDV_i, of the two alternative regulatory regimes ($i=GenEd$, GMO). It goes as follows:

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[2] This setup potentially multiplies the number of cases to analyze, depending on the speed of adjustment, the reaction of the market which could be influenced by labelling requirement etc. Here, we focus on a central case. The Excel simulation tool utilized for the 3 case-studies is available from the authors. It allows variations in parameters (a,b, k), discount rate r, and levels of future annual benefits, B (see equations (2) and (3)).

$$PDV^{GenEd} = \sum_{t=1}^{T} \frac{1}{(1+r)^t} (B_t^{GenEd} P_t^{GenEd} - C_t^{GenEd}), \ (2)$$

$$PDV^{GMO} = \sum_{t=1}^{T} \frac{1}{(1+r)^t} (B_t^{GMO} P_t^{GMO} - C_t^{GMO}), \ (3)$$

$$Savings = PDV^{GenEd} - PDV^{GMO}. \ (4)$$

The per period discount rate is *r*. Discounting later periods makes the arbitrary choice of the end point *T* less pivotal and reflects the preference for payoffs earlier rather than later. The discounting rate *r* is set here at 4% per annum as in the Van Eenennaam et al. analysis. Other discounting rate values can be used, but 4% is recognized in the literature as an acceptable central value (Newell and Pizer, 2003). We compute the present discounted values *PVD*, of the innovation under the two regulatory regimes for time horizon *T*. The three elements of the *PDV*, costs *C*, benefits *B*, and rate of adoption *P* are characterized by superscript *j* for *j=GenEd*, *GMO*. The innovation has front-loaded cost and then generates benefits post approval. The two regulatory and commercialization stages have different costs and timeframes under the two regulatory regimes. We follow with the three case studies.

3. First Case Study based on Expert Opinion

In the first empirical case, we calibrate adoption parameters *a* and *b* in equation (1) to be consistent with the expert opinions collected and aggregated in Lassoued et al. (2019) and to reach an adoption rate of 50% (parameter *k*=0.5 in (1)). The Lassoued et al. estimates of cost and duration are based on expert opinions elicited through a survey. Under the conventional regulation, these authors report that the Commercialization step takes 1 year and costs \$2 million. Under the GMO regulation, Commercialization takes 3 years and costs \$5 million. The higher cost and longer duration are motivated by more resistance, and down-market from potential wary consumers and processors. In addition, because of the delay in regulatory approval, Commercialization takes place later in the case of GMO regulation.

Approval under conventional-hybrid regulation lasts one year and costs US$2 million, whereas under GMO approval, it is a 5-year process at an average estimated cost of $9 million (Lassoed et al. (2019)). Time zero indicates the beginning of the innovation process. For GMO-regulated innovations, N_{GMO} is 8 (1.5+1.5+5), as reported by Lassoued et al. (2019), and N_{GenEd} is at the end of year 4 (1.5+1.5+1) for GenEd innovations. The regulatory processes take 5 years (GMO) and 1 year (GenEd) for these two types of regulations.

Table 1, adapted from Lassoued et al. (2019), summarizes the timing and costs used in calibrating the first case study. It highlights the differences in cost and duration between GenEd and GMO regulatory regimes. The table assumes that the first two steps in the innovation process are identical, irrespective of the regulatory regime. See steps "Research/Discovery/Conception" and "Development/Implementation." These relate to the scientific discovery steps. The GenEd R&D process takes two steps of 1.5 years each and costs $6.5 million in total. Then the regulatory approval and commercialization steps diverge under the different regulations, one following the GenEd rapid and more economical approval, and commercialization. The other regime is longer and costlier for both approval and market launch steps under the GMO regime. Benefits of the innovation get delayed by 10 years under the GMO-regulation compared to the GenEd regulatory regime.

The assumptions underlying the first simulation are summarized in Table 2. The smaller value for parameter b under the GMO regulation reflect the slower adoption process under a GMO regulation. Simulation results for this first case are summarized in Table 3. If no benefit is considered, the net savings from treating a representative GenEd innovation as a conventional-hybrid plant innovation (as opposed to treating it as GMO) are above $7 million, including both delays and costs differences for approval and commercialization. The framework is simple but provides a clear way to integrate cost and time differences in a consistent framework.

Table 1. Estimated cost and time involved in getting genome-edited crops to market (mean values) under two regulatory regimes. Generic case based on Lassoued et al.

	GenEd regulated as conventional hybrid						GenEd regulated as GMO					
	Cost			Time			Cost			Time		
R&D stages	US$M	SD*	%	Years	SD	%	US$M	SD	%	Years	SD	%
Research/Discovery/Conception	3	4.11	29	1.5	1.10	30	3	4.11	15	1.5	1.10	14
Development/Implementation	3.5	4.75	33	1.5	1.27	30	3.5	4.75	17	1.5	1.27	14
Regulatory Activity/Authorization	2	3.25	19	1	.88	20	9	1.17	44	5	3.03	45
Launch/1st Commercial Sale	2	2.79	19	1	.89	20	5	5.71	24	3	2.22	27
Total	**10.5**		**100**	**5**		**100**	**20.5**		**100**	**11**		**100**

Source: Lassoued et al. (2019) adapted for our analysis. Calibration spreadsheet available from the authors.*SD stands for standard deviation

Table 2. Parameters assumptions for case study #1

Time	t	1 through 30
Logistic parameters	a	-7.0
	b^{GenEd}	12.0
	b^{GMO}	4.0
Share of adopters	k	0.5
Discount rate	r	4%
Annual benefit per innovation	B_t	See range in Table 3

Table 3. Simulations results for case study #1 (in US$ million)

PDV^{Gened}	-9.37	-2.54	4.28	11.11	17.94	24.77
PDV^{GMO}	-16.52	-11.67	-6.82	-1.97	2.89	7.74
Cost savings under GenEd regulation	7.15	9.13	11.10	13.08	15.06	17.03
Annual gain posited (B_t)	$-	$1.00	$2.00	$3.00	$4.00	$5.00

As annual benefits kick in, the saving under the lighter regulatory approach increases as delays penalize the start of the benefit accruing under the GMO regime. Delays also increase the discounting because benefits are pushed further in the future under the GMO regime.

Next, we consider the breakeven point under the two regimes, which corresponds to a zero *PDV* over the 30-year timespan. The breakeven point is the annual future benefit level B_t

which equates the discounted value of future cost and future benefits over the determined time (30 years here). We obtain \$1.37 Million under the GenEd regulatory regime and \$3.41 Million under the GMO regime, with their ratio equal to 2.48. The ratio says that the breakeven revenue must be roughly two and a half times as large if the innovation is regulated as a transgenic product rather than as a conventional-hybrid breeding innovation.

Note that the Lassoued et al. analysis provides consensus estimates of duration and cost by experts and relates to a panel of various products, predominantly row crops. These are not tied to specific regulatory agencies. The experts came from countries members of the Organization for Economic Cooperation and Development (OECD). The predominance of row crops is a limitation given the longer durations involved in tree crops and woody vining plants.

4. Second Case Study Based on Summary Data of Agro-Chemical Firms

In this second case study, we follow a similar approach to the first case study on adoption but with new data on cost and duration and some additional assumptions for what happens under the GenEd regulatory environment leading to avoidable costs. The cost of regulatory approval in AgbioInvestor (2022) assumes that for the plant having a new trait of interest, cultivation approval is obtained in at least two countries, and importation approval in at least five countries. The analysis distinguishes consecutive time requirements and steps that can overlap over time, an important consideration for GenEd obtained traits as well. These are summarized in Table 4.

Table 4. Cost and duration of a GMO innovation up to market adoption from AgbioInvestor (2022) and authors' assumptions for the GenEd duration

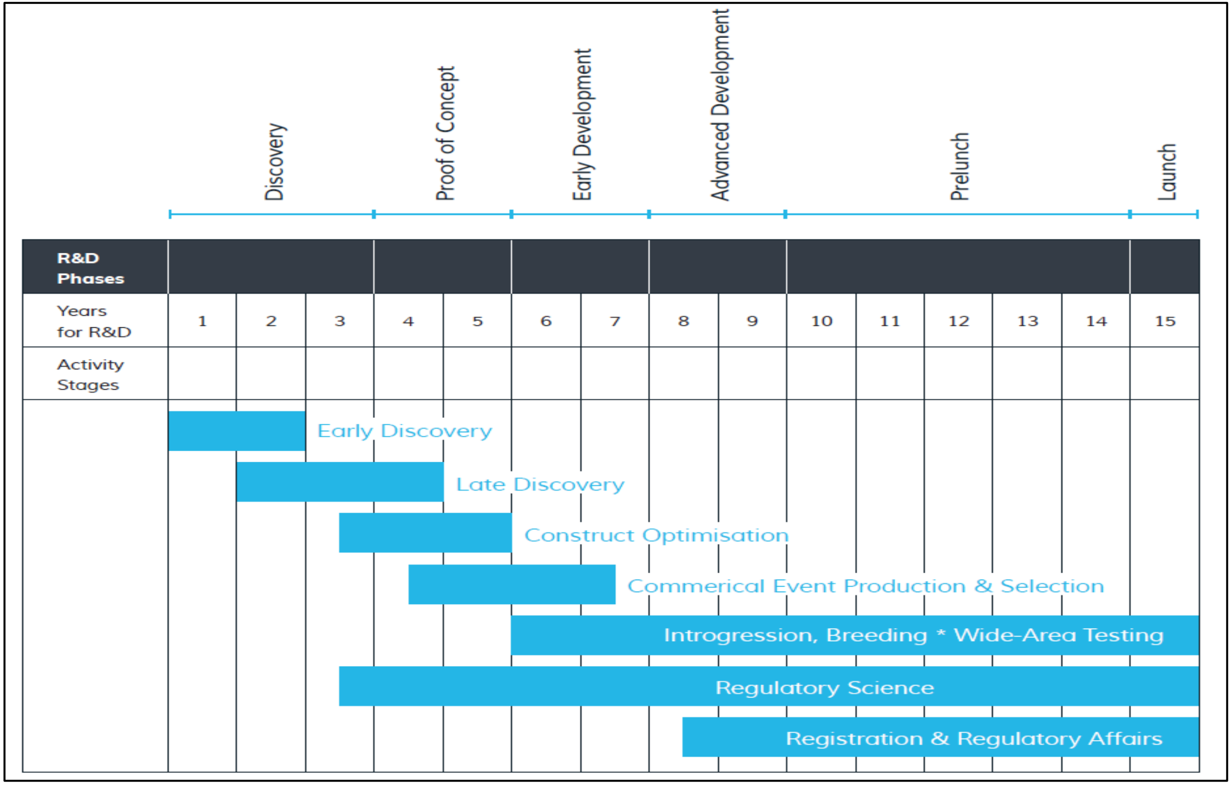
	GMO regulation		**GenEd regulation**	
Activity Stage	**Cost (\$ m.)**	**Duration (months)**	**Cost (\$ m.)**	**Duration (months)**
1. Early Discovery	2.8	25.5	2.8	25.5
2. Late Discovery	4.8	27.7	4.8	27.7
3. Construct Optimization	13.4	28.6	13.4	28.6
4. Commercial Event	21.8	35.3	21.8	35.3

Production & Selection				
5. Introgression, Breeding & Wide-Area Testing	29	78.6	14.5	39.3
6. Regulatory Science	32.9	112.2	3.5	12
7. Registration & Regulatory Affairs	10.3	92.4	1.3	12
Total	115	400.1	62.2	180.4

Steps called Regulatory Science and Registration and Regulatory Affairs cost \$32.9 and \$10.3 million, based on data for the years 2017-2022 collected by four major biotech global companies (Bayer Crop Science, Corteva Agriscience, Syngenta, BASF Agricultural Solutions). In terms of time requirements, Regulatory Science takes 112.2 months, and Registration and Regulatory Affairs take 92.4 months. The Regulatory-Science step starts roughly in year 2.5 and lasts to the end of the 15 years (around 9.5 years duration); Registration and Regulatory Affairs starts mid-year 8 and lasts 7.7 years. Introgression and Wide Area Testing also lasts till the end of the process after having started in year 6.

We follow the structure of Figure 1 to establish the sequence of steps and their overlap under the GMO regulation. We focus on the Regulatory Science step and the last stage, Registration and Regulatory Affairs. We assume that the various stages are at times consecutive but can overlap as suggested in Figure 1. The detailed stages and months allocated are shown in Table 5. We note that in AgBioInvestor, the regulatory step, even with its overlap, lasts 12.5 years, which is longer than Lassoued et al. (5 years) and costs much more (\$43.2 million in AgBioInvestor versus \$9 million in Lassoued et al.). Duration and cost information shown in Table 4 is used along with parameters of Table 2 to calibrate the second case study. For the GenEd columns in Table 4, we assume that the first four stages (Early and Late Discovery, Construct Optimization, and Commercial Event Production & Selection) are identical for GenEd and GMO alternatives. The difference between the 2 alternatives starts with stage 5.

Figure 1. Example of nonconsecutive duration of R&D process for GMO innovation



Source: AgbioInvestor (2022).

Better targeting of modification or gene introduction under GenEd reduces the stage of Introgression and Breeding, and Wide Area Testing. Wide Area Testing may be reduced or not required. We assume that duration of this 5th stage is reduced by half in the GenEd case. Stages 6 and 7 are reduced to 12 months each at the same monthly cost corresponding to the GMO monthly cost per stage. These assumptions for stages 6 and 7 are in the vicinity of time required for Regulatory Activity and Authorization in Lassoued et al. (1 year). As a result, The GenEd process takes 10 years to get to start market adoption, whereas the GMO case takes 15 years and higher cost to reach the market adoption stage. We also assume a delay in the adoption of the GMO innovation as in the first case study because of user reluctance, which has been documented multiple times over the last twenty years (Beghin and Gustafson, 2021; Lusk et al., 2005).

Table 5. Stages and overlapping of stages for GMO and GenEd innovations based on AgBioInvestor(2022)

Agbioinvestor 2022 datafor R&D innovation process																					
years	1	2	3	3.5	4	4.5	5	6	6.5	7	7.5	8	9	10	11	12	13	14	15	16	30
stages GMO with months	Early discovery 12	Early discovery 13.5/late discovery 12	Early discovery 1.5late discovery 12+ construct 4.6	Late discovery 3.7 /construct optimization 6	Construct optimization 6/reg science 0/ commercial event production 6	Construct optimization 6/commercial event production /selection 6/reg science 0	Construct optimization 6/commercial event production 6/selection/ reg science 6	commercial event production 12 /selection/Introgression breeding wide area testing 12/reg science 12	Commercial event production/selection 5.3/Introgression breeding wide area testing 6 /reg science 6	Introgression breeding wide area testing 6 /reg science 6	Introgression breeding wide area testing 6 /reg science 6 /registration & reg affairs 0	Introgression breeding wide area testing 6/reg science 6 /registration& reg affairs 8.4	Introgression breeding wide area testing 12/reg science 12 /registration & reg affairs 12	Introgression breeding wide area testing 12/reg science 12 /registration& reg affairs 12	Introgression breeding wide area testing 12/reg science 12 /registration & reg affairs 12	Introgression breeding wide area testing 6.6/reg science 12 /registration & reg affairs 12	Introgression breeding wide area testing 0/reg science 12 /registration & reg affairs 12	Introgression breeding wide area testing 0/reg science 12 /registration & reg affairs 12	Introgression breeding wide area testing 0/reg science 0 /registration & reg affairs 12	market adoption	market steady
cost from stage GMO in Million dollars	$ 1.32	$ 3.56	$ 4.40	$ 3.45	$ 6.52	$ 6.52	$ 7.75	$ 15.36	$ 7.25	$ 3.97	$ 3.97	$ 4.64	$ 9.28	$ 9.28	$ 9.28	$ 7.29	$ 4.86	$ 4.86	$ 1.34	$ -	$ -
stages GenEd with months	early discovery 12	early discovery 13.5/late discovery 12	late discovery 12+ construct 4.6	late discovery 3.7 /construct optimization 6	construct optimization 6/reg science 0/ commercial event production 6	construct optimization 6/commercial event production /selection 6/reg science 0	construct optimization 6/commercial event production /selection 6	commercial event production 12 /selection/Introgression breeding wide area testing 12/	commercial event production/selection 5.3/Introgression breeding wide area testing 6	Introgression breeding wide area testing 6	Introgression breeding wide area testing 6	Introgression breeding wide area testing 6/	Introgression breeding wide area testing 3.3/12 reg science	/registration& reg affairs 12	market adoption	market adoption	market adoption	market adoption	market adoption	market steady	market steady
cost of each stage gened in million dollars	$ 1.32	$ 3.56	$ 4.40	$ 3.45	$ 6.52	$ 6.52	$ 5.99	$ 11.84	$ 5.49	$ 2.21	$ 2.21	$ 2.21	$ 4.74	$ 3.52	$ -	$ -	$ -	$ -	$ -	$ -	$ -

The logistic parameters of Table 2 are maintained for this second case study. Table 6 shows simulation results for various levels of assumed annual revenues over 30 years of time.

Table 6. Cost savings from regulatory regime change (in $Millions) for case study #2

PDV^{GenEd}	-$51.70	-$5.78	$40.14	$86.06	$131.98
PDV^{GMO}	-$85.85	-$58.21	-$30.57	-$2.92	$24.72
cost savings with proper PDV in million dollar	$34.15	$52.42	$70.70	$88.97	$107.25
Posited annual gains in $million	$-	$10.00	$20.00	$30.00	$40.00

Breakeven revenues per year for the GenEd regulatory regime is $11.26 million. That is much higher than in the Lassoued et al. case study for which cost figures were one order of magnitude smaller. The breakeven for the GMO regime is $31.06 million. Their ratio (31.06/11.26) is 2.76, which is close to the ratio in the first case study (2.48). In sum the GMO regulation regime considerably inflates the breakeven revenue value relative to the regulatory regime treating GenEd as conventional hybrid.

5. Third Case Study on Grape for Wine Production

This third case study is unlike the other two previous ones. It specifically relates to grape or grapevine for winemaking, using information in France on new wine varietal approval system in France and the EU and the EU regulatory framework on genetic research. The case dives into more details which are summarized in Appendix 1. The science of GenEd innovations in grapes for winemaking is developed in detail in This and Beghin (2023).

Innovations in grapes for wine making tend to come slowly. Even with advanced genetic techniques, on average, it takes 20 years or more to create and bring an innovated grape or grapevine into a variety to market. For that reasons, R&D seems to be dominated by public-sector researchers rather than innovating firms.[3] Because of the time it takes for grapevines to produce mature fruit, the timeline for producing valuable innovations through GenEd is close to that of its conventional counterpart. This is similar to apples R&D (lengthy and undertaken mostly by public-sector actors). R&D in grapes (as for apples) in the EU tends to eschew transgenic research (Lemaire et al., 2010; and Marette et al., 2023a), given the reluctance of many stakeholders toward biotechnology. We note that biotechnology in grapes for wine has been much more active in other regions (Lemaire et al. (2010)). The latter authors report 60 GMO grape events occurring in the US, Canada, and Chile from 1995 to 2010.

GenEd based innovations could reduce the duration of some of these steps and ease the process of selecting interesting hybrids. It is hard to find such evidence nevertheless despite the promising relevance of GenEd in grapes (Deluc and Gouthu, 2018; Gouthu and Deluc, 2022; and Dalla Costa et al., 2019). The key differences between the two regulatory regimes currently identified are the delays in the approval process under a GMO regime (see Appendix 1 on the process and Appendix 2 on EFSA approvals). and the additional and costly field trials with GMOs. Some moderate cost increases also take place because of greenhouse requirements and field protections under the GMO regulatory regime.

In the EU context, the possibility of field destruction by some GMO opposing groups is a real possibility (LeMaire et al., 2010; Chauveau, 2010). We account for the higher cost to protect fields and greenhouses against destruction by anti-GMO groups. Former CEO of INRA Guillou cites €1 million invested between 2005 and 2010 for 5 years being lost in 2010 in Colmar after the destruction of the GMO experiment (Chauveau, 2010).

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[3] In this case study we limit our analysis to genetic editions of existing varieties used in wine and exclude the case of cisgenesis based on wild species of vinifera. The latter introduction would take much longer, especially in the regulatory step establishing the new variety for wine making.

One can decompose the science in GenEd R&D in grapes grown for wine into 5 scientific steps summarized in Table 7, before the approval and commercialization steps. The Table considers three alternatives (an innovation leading to a new cultivar under GenEd/conventional-hybrid regulation, a clone leading to the same variety under GenEd/conventional-hybrid regulation, and a new cultivar under GMO regulation). Duration and cost estimates are provided. The research steps are explained in more detail in Appendix 1. This is a sequence of steps going from new plant constructs in the lab to field trials to the eventual approval and registration of the new variety. Steps 1 through 3 are identical in duration and science under the 3 possible alternatives, although greenhouse costs are higher under the GMO regime. Here we assume that the engineering of the new grapevine construct takes 6 months, but it could take longer depending on the traits of focus.

Next, in the fourth step (stage 2), the alternatives diverge. Under the conventional-hybrid regulation for a new variety, step 4 takes 6 years and involves 1 site. The same new cultivar under GMO regulation also takes 6 years but with slightly higher costs. For a clone, this 4th step is lengthy (12 years) because of long term test on the same single site. The 5th step (Stage 3) is the multi-site step for the new variety. The conventional-hybrid regulatory environment would require 3 sites and last about 6 years. Under the GMO regulation, more field trials are required as well as more testing (8 sites instead of 3 sites under conventional-hybrid regulation). All field trials under GMO regulation exhibit a higher cost because of special field preparation and protection. After these 5 research steps, approval would be required by a GMO regulation. We add the lengthy and costly approval step by EFSA. The new variety under conventional hybrid or GMO regulation would also involve the Inscription and Performance test step to get the new variety registered.

If a clone is developed rather than a new variety, Stage 3 (multisite trails) is not required but the 2d stage is extended to 12 years on the single site (at a cost of $1,232,196), which is lower than for the new variety when comparing the sum of stages 2 and 3 for the new variety. The savings are roughly $292,000. The clone variety does not require the Inscription and Performance test, which is the second source of savings (2 years and $100,000).

Table 7. Steps involved in R&D in grapevine with duration and cost

Steps	Duration in years conventional hybrid regulation new variety	Cost in $ conventional hybrid regulation new variety	Duration in years conventional hybrid regulation clone	Cost in $ conventional hybrid regulation clone	Duration in years GMO regulation	Cost in $ GMO regulation
1. Laboratory identification	0.5	84,678	0.5	84,678	0.5	84,678
2. Stage 1 in vitro culture	1.5	334,453	1.5	334,453	1.5	334,453
3. Stage 1 greenhouse	3.0	544,011	3.0	544,011	3.0	615,084
4. Stage 2 field trial	6.0	616,098	12.0	1,232,196	6.0	621,940
5. Stage 3 multilocation field trial	6.0	903,167	0	-	6.0	2,429,217
6. GMO EFSA approval	0.0	-	0.0	-	4.0	400,000
7. Inscription and performance	2.0	100,000	0	-	2.0	100,000
Total	19.0	2,582,407	17.0	2,195,338	23.0	4,585,371

We abstract from various small fees described in the appendix, but we account for the research infrastructure and staff time involved and costly trials per site and number of sites. These are accounted for in the excel folder (see Table 6 details sheet) accompanying the manuscript.

For the PDV calibration in this third case study, we keep assumptions of the first case studies on discounting and adoption (see Table 2), except that we extend the time period to 35 years to allow for time to generate benefits/revenues. The R&D process is long for grapevine under both regulatory regimes (19 and 23 years). The 30-year horizon would not allow us to generate substantial revenues. Note that discounting after 35 years becomes substantial. It removes about 75% of the future annual benefits in the PDV. Adding more years to the horizon would increase the PDV at a decreasing rate given the increasing discounting.

Table 8 shows the results of the calibration and simulations of the PDVs under various annual benefit levels, from none to $2.5 million, and for the new variety under conventional-hybrid regulatory regime and GMO regulatory regime. The clone case leads to qualitatively similar results and is available upon request.

Table 8. PDVs and Savings under different benefit levels for grapevine R&D (in 1000$)

Annual benefits	0	500	1,000	1,500	2,000	2,500
PDV GenEd	-1,758	- 376	2,999	2,388	3,770	5,152
PDV GMO	-2,868	-2,035	-1,202	-369	465	1,298
Savings (GMO-GenEd)	1,110	1,1,659	2,208	2,756	3,305	3,854

The ratio of the PDV under no annual benefit is 1.63. The savings are significant ($1.110 Million). Table 7 shows that a high level of annual benefit is required to have the R&D financially successful, independently of the regulatory regime, because of the lengthy nature of grapevine research. The GMO regulatory regime exacerbates this element. The breakeven values (PDV=0) are $0.636 million if the innovation is treated as a conventional-hybrid breeding innovation, and $1.721 million under the GMO regulatory regime. Their ratio is 2.71, showing again a more-than-doubling of the required annual benefit to break even under the GMO regime. This relative magnitude is quite comparable to the those of the two previous case studies.

6. Conclusions

We undertook three case studies using a PDV approach accounting for costly delays, cost and duration estimates of R&D from initial research to market adoption and using three different sources of information. We also accounted for the market launch of the innovation leading to a long-term stable participation under both regulatory regimes. The three cases were based on recent ex-ante expert opinion for a large set of staple crops, on actual R&D experience of four large global biotechnology companies for important row-crop commodities, and a new analysis of the grape R&D process in France developed for this project.

The substantial regulatory approval delays experienced in GMO R&D are reflected in these case studies and drive the key qualitative results, leading to much added cost and further discounting of future benefit. Although the absolute costs varied widely across the case studies, the relative costs showed that regulating GenEd as transgenic GMOs increases costs by 63% to 76%. In addition, we obtain a large range of breakeven values but a much narrower range of relative values (between 2.48 and 2.76) indicating that viable GenEd innovations would have to be drastically more profitable if they are treated as GMOs.

Industrial organization varies across the case studies. The first case study covers a wide range of staple crops and products reflecting different market organizations. The second case study reflects the dominance of large global firms in commodity markets and their focus on return to R&D. The third case reflects the non-profit nature of grapevine R&D in Europe and its lengthy and slow discovery process. Grapevines take years to reach maturity unlike row crops.

The analysis also considered the impact on international trade, highlighting the challenges posed by asynchronous regulatory regimes. The second case study was under the assumption of an approval for planting in two countries and imports in five different countries.

The first case study did not specify how many markets were implicitly considered but one can easily derive the implications of asynchronous regulations across borders, when one country regulates GenEd innovations as conventional-hybrid breeding and another as a GMO innovations. The contrast in costs and breakeven values implies that trade of these innovations will be impeded by asynchronous regulations requiring a GMO approval in some markets and GenEd/conventional hybrid approval in others. The rate of innovations is likely to suffer when market size for these new products shrink because of asynchronous approval or heterogeneous regulatory environments, as shown in Marette et al. (2023b). The third case is in the context of the custom union of the European Community which provides scale for innovation in such a large market. Even in that case, the dependence of the EU wine industry on exports would induce similar challenges with heterogenous regulations between the EU and exports markets.

References

AgbioInvestor. (2022). Time and Cost to Develop a New GM Trait. A Study on Behalf of Crop Life International. https://croplife.org/wp-content/uploads/2022/05/AgbioInvestor-Trait-RD-Branded-Report-Final-20220512.pdf

Bayer JC, Norton GW, Falck-Zepeda J. (2010). Cost of compliance with biotechnology regulation in the Philippines: implications for developing countries. *AgBioForum* 13:53–62.

Beghin, John C., and Christopher R. Gustafson. (2021). "Consumer valuation of and attitudes towards novel foods produced with new plant engineering techniques: A review." *Sustainability* 13, no. 20 (2021): 11348.

Bruetschy, Chantal. "The EU regulatory framework on genetically modified organisms (GMOs)." *Transgenic research* 28, no. Suppl 2 (2019): 169-174.

Chauveau, J. (2010). Interview. « Les faucheurs d'OGM ont handicapé la capacité d'expertise de la recherche publique » (Marion Guillou -INRA). Les Echos le 17 août 2010.

Dalla Costa, L. M. Malnoy, D. Lecourieux, L. Deluc, F. Ouaked- Lecourieux, M. Thomas, L.J.M Torregrosa. (2019). The state-of-the-art of grapevine biotechnology and new breeding technologies (NBTS). *OENO One*, 2019, 53 (2), pp.189-212.

Deluc, L., and S. Gouthu. (2018). “Applications of the CRISPR Technology for the Wine Industry.” Abstract. American Society for Enology and Viticulture.

European Food Safety Authority (EFSA) (2021). GMO application procedure - an overview. https://www.efsa.europa.eu/en/applications/gmo accessed June 2023.

European Parliamentary Research Service. (2022). Genome-edited crops and 21st century food system challenges. STOA PE 690.194-July 2022.

EU-SAGE. European Sustainable Agriculture through Genome Editing. (2023). https://www.eu-sage.eu/genome-search?f%5B0%5D=Genome_Editing_Technique%3ACRISPR/Cas&f%5B1%5D=plant%3AGrapevine%20%28Vitis%20vinifera%29 (accessed November 2023).

Falck-Zepeda J, Yorobe J Jr, Husin BA, Manalo A, Lokollo E, Ramon G, Zambrano P, Sutrisno. (2012). Estimates and implications of the costs of compliance with biosafety regulations in developing countries. *GMCrops Food*. 3(1):52–59. Epub 2012/05/23. doi:10.4161/gmcr.18727. PubMed PMID: 22614639.

Gouthu, S., and L. Deluc. (2022). ”Developing a Method for Making Transgene-Free Gene-Edited Grapevines” abstract. American Society for Enology and Viticulture.

Kalaitzandonakes N, Alston JM, Bradford KJ. (2007). Compliance costs for regulatory approval of new biotech crops. *Nat Biotechnol*. 25:509. doi:10.1038/nbt0507-509.

Lassoued, R., Phillips, P. W., Smyth, S. J., & Hesseln, H. (2019). Estimating the cost of regulating genome edited crops: expert judgment and overconfidence. *GM Crops & Food,* 10(1), 44-62.

Lemaire O, Moneyron A, Masson JE. (2010). “Interactive Technology Assessment” and Beyond: the Field Trial of Genetically Modified Grapevines at INRA-Colmar. *PLoS Biol* 8(11): e1000551. https://doi.org/10.1371/journal.pbio.1000551

Lusk, Jayson L., Mustafa Jamal, Lauren Kurlander, Maud Roucan, and Lesley Taulman. (2005) "A meta-analysis of genetically modified food valuation studies." *Journal of agricultural and resource economics* vol 30 (1): 28-44.

Marette, S., J. Beghin, A.C. Disdier, and E. Mojduszka. (2023a). "Can foods produced with new plant engineering techniques succeed in the marketplace? A case study of apples." *Applied Economic Perspectives and Policy* 45, no. 1 (2023): 414-435.

Marette, S., Disdier, A.C., Bodnar, A. and Beghin, J., (2023b). New plant engineering techniques, R&D investment and international trade. *Journal of Agricultural Economics* 74(2): 349-368.

McDougall P. (2011). The cost and time involved in the discovery, development and authorisation of a new plant biotechnology derived trait. A Consultancy Study for Crop Life International September. CropLife International; https://croplife.org/plant-biotechnology/regulatory-2/cost-of-bringing-a-biotech-crop-to-market

Montaigne, E., A. Coelho, and L. Khefifi. (2016). Economic issues and perspectives on innovation in new resistant grapevine varieties in France. *Wine Economics and Policy*, 2016, 5, pp.73-77.

Newell, Richard G., and William A. Pizer. (2003). "Discounting the distant future: how much do uncertain rates increase valuations?" *Journal of Environmental Economics and Management* 46, no. 1: 52-71.

Pray CE, Ramaswami B, Huang J, Hu R, Bengali P, Zhang H. (2006). Costs and enforcement of biosafety regulations in India and China. *Int J Technol Globalisation*. 2006; 2(1–2):137–57.

doi:10.1504/ijtg.009131.

Pray CE, Bengali P, Ramaswami B. (2005). The cost of biosafety regulations: the Indian experience *quarterly. J Int Agric*. 44: 267–89.

Smart RD, Blum M, Wesseler J. (2017). Trends in approval times for genetically engineered crops in the United States and the European union. *J Agric Econ*. 68(1): 182–98. doi:10.1111/1477-9552.12171.

This, P. (2022). Slides from guest lecture of 2022. Personal communication.

This, P and J. Beghin. (2023). "The potential of genome editing for the viticulture and wine industry." Mimeo. Report to USDA FAS. November 2023.

Wesseler, J., Smart, R.D., Thomson, J. and Zilberman, D., 2017. Foregone benefits of important food crop improvements in Sub-Saharan Africa. *PLoS One*, *12*(7): e0181353.

Van Eenennaam, A. L., De Figueiredo Silva, F., Trott, J. F., & Zilberman, D. (2021a). Genetic engineering of livestock: the opportunity cost of regulatory delay. *Annual Review of Animal Biosciences*, *9*, 453-478.

Van Eenennaam, De Figueiredo Silva, Trott, and Zilberman. (2021b) Supplemental Material: *Annu. Rev. Anim. Biosci*. 2021. 9. https://doi.org/10.1146/annurev-animal-061220-023052 Genetic Engineering of Livestock: The Opportunity Cost of Regulatory Delay.

Vivai Cooperativi Rauscedo (VCR) 2022. The resistant generation. online document: https://www.vivairauscedo.com/contributi/download/stato-dell-arte-2022-en.pdf

Appendix 1. The R&D and regulatory steps for biotechnology innovations in grapevines

The incentive structure

The path for incentivizing R&D in Vines/grapes for wine production in France and Europe is different than for row crops. Most of the innovation and R&D in grapevine is done by non-profit public entities such as INRAE. Nevertheless, the rent-seeking and political economy surrounding R&D in agriculture does create incentives to increase funding in the public sector and using biotechnology despite some societal concerns. A strong coalition of researchers, large private agricultural and agribusiness interests are pushing for new breeding techniques to be approved as conventional hybrid crops to simplify and for research to be well-funded (European Parliamentary Research Service, Dalla Costa et al., 2019, Deluc and Gouthu, 2018, and Gouthu and Deluc, 2022). Private R&D in grapevines for wine production is limited. There is Vivai Cooperativi Rauscedo (VCR) in Italy involved in improvements through hybridization with conventional hybrid methods rather than GenEd techniques (VCR, 2022), and Mercier nursery in France. The public research funding is stable and is less sensitive to the variation in return to biotech R&D. However, it still makes sense to look at returns and benefit stream and breakeven levels of benefits to gauge the implications of regulating GenEd R&D as GMO rather than conventional hybrid breeding.

This roundabout process via stakeholders rather than via profitable R&D is likely to lead to regulations which will be more sensible than those for GMOs and to well-funded research in the public sector. This is different from a private-sector model in which more profitable R&D with favorable regulation will lead to higher level of investments in R&D or dry out if profitable prospects look dim with stringent regulation. In grapevines, the public research funding is assured and is less sensitive to the variation in return to biotech R&D. It could still be sensitive to the lengthy approval process.

Description of required steps under GenEd for clone of existing varieties, or for new varieties
For GenEd plants, the procedure will be different depending on whether they are considered clones of edited varieties or new varieties, but the duration for both situation is the same (144 months). Appendix Table 1 summarizes the duration of the steps.

Appendix Table 1. Duration of grapevine research steps from construct before approval

Science Stage #	Stage 0	Stage1		stage2	stage 3	Approval
Step description	**Engineering of constructs**	**in vitro culture**	**greenhouse**	**field trial**	**multilocation field trial**	**Regulatory step**
Duration for clone	6 months	12-18 months	36 months	144 months	NA	NA
Duration for new cultivar as GenEd	6 months	12-18 months	36 months	72 months	72 months	NA
Duration for New cultivar as GMO	6 months	12-18 months	36 months	72 months	72 months	48 months approximated (Appendix 2)

Clones: If they are considered clones, the approval process is simpler. The idea is that the grape variety is already known, and the clone is just a small variation of the grape variety. It replaces the steps of stages 2 and 3 for varieties (indicated in the Excel table). Longer tests take place in a single site and there is no need for multi-site testing. First, there is a check for the health status, lasting 2 years (2 growing seasons). However, if we edit an approved clone from healthy material, we might be able to skip this step, considering that the main part of the procedure is in the laboratory or greenhouse.

The second step is an agronomic and technological step. It involves establishing a collection of clones from the base material (original plants). This depends on the grape variety. Since the procedure will initially be performed with the most used grape varieties, those with many clones, the clone collection should include 2 to 3 control clones + the edited clones, with 6 repetitions of a minimum of 5 plants each, all 30 in one location. Measurements begin 4 to 5 years after planting and last for 5 years, resulting in a 10-year study. In total the process is 12 years for the health status combined with the 10-year study.

The third step is an identity verification using molecular markers, which can be done during the first two steps, and the cost is negligible. So, we do not vary our cost estimate for this feature.

New Variety: If the edited plant is considered a new variety, the procedure follows a longer process with stages 2 and 3 as described in the supplemental Excel folder accompanying the manuscript. here we focus on the steps required in France. There are additional steps to establish the variety in the EU-27 through the Community Plant Variety Office (CPVO). CPVO is a European Union agency establishing and protecting plant variety rights for the 27 Member States. The process is lengthy for fruit trees and grapevines (up to 6 years). We abstract from this step in this analysis. several of the steps to get the variety approved in France get be used in the CPVO process.

Stage 2 requires a minimum of 10 plants per variety, a study over two years, after 3 to 4 years of planting, hence a total duration of 6 years. Stage 3 requires multilocation trial used for the VATE.[4] Sanitary tests are fast (PCR or Elisa) and have limited costs (a few hundred euros). Next is a rooting/grafting aptitude test, which anyway is necessary to produce the plants that will be planted for the VATE. It is to be conducted with at least 100 grafts for 3 different assemblies with 3 different rootstocks. The duration to obtain grafted plants is 1 year. The cost is estimated at 2 to 3 euros per graft, totaling around €1000 per registered variety. This is a small cost compared to the human resource costs.

If resistant or tolerant varieties are registered, tests must be conducted by an accredited laboratory, which charges for the service. However, this is done simultaneously with the VATE tests. If editing affects a specific trait such as drought tolerance, a specific experiment may be required, testing the varieties under different water regimes, with additional costs: installation of irrigation or water exclusion systems, and doubling the areas.

Observations and measurements take place over a minimum of three years of normal production, starting no earlier than the second year following planting (3rd leaf), totaling at least 5 years + one year of preparation for grafted plants, at least 6 years in total.

The trial network includes at least two locations, representative of the production basins for which the varieties are intended. Each trial includes at least one catalog-listed control variety well adapted to local conditions. The devices used (complete randomized blocks) involve at least 3 repetitions, and the total number of plants per variety modality (control(s) and requested variety(ies)) must not be less than 90. Therefore, two repetitions of a minimum of 90 plants (3 blocks of 30 plants) + at least one control variety under the same conditions are required. If testing multiple new varieties, this additional cost is spread out. The two repetitions are a minimum, and depending on the variety, if it is intended for use in a very specific area, it might suffice. However, for a more widely spread grape variety, more repetitions might be necessary.

For the variety registration, the DHS (Distinctiveness, Homogeneity, and Stability) test is also required. The test is done on about ten plants. You have to wait for 3 years, and then the tests last for 2 years, making a total duration of 5 years. To expedite the procedure, this can be done simultaneously with the VATE. This additional cost is assumed to be small, and we abstract from it. Note that the CPVO has a corresponding test (Distinct, Uniform, and Stable or DUS test). Presumably, the French DHS test can be used for the DUS test.

GMO-regulated innovation

If you have a variety considered as a GMO, the same tests apply as above for the new variety, and in addition, specific tests for GMOs must be conducted. This includes at least the 8

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[4] VATE means Valeur Agronomique Technologique et Environnementale (for row crops and grapes). These VATE criteria are criteria for quality and improvements which have to be met by the proposed variety in review.

multilocation tests for phenotypic and agronomic characterization, as well as tests related to potential risks for human health and the environment (as presented in the figures shown below). These additional tests have never been done, but we still believe that the tests for phenotypic and agronomic characterization could be useful for the VATE. To estimate this cost, we scale up the amount estimated for the GenEd regime from 3 sites to 8 sites.

However, estimating potential environmental risks also requires field experiments with specific constraints, so we believe these are separate and additional trials. The environmental risk assessment needs fields trials to check (i) the persistence and invasiveness including plant-to-plant gene flow, (ii) the environmental impact of GMO on population levels of herbivores, natural enemies, symbionts (where applicable), parasites, and pathogens not target of the newly expressed metabolites, and (iii) the effects on biogeochemical processes i.e., movement, transformation and storage of energy, water, carbon, nitrogen and other elements in ecosystem.

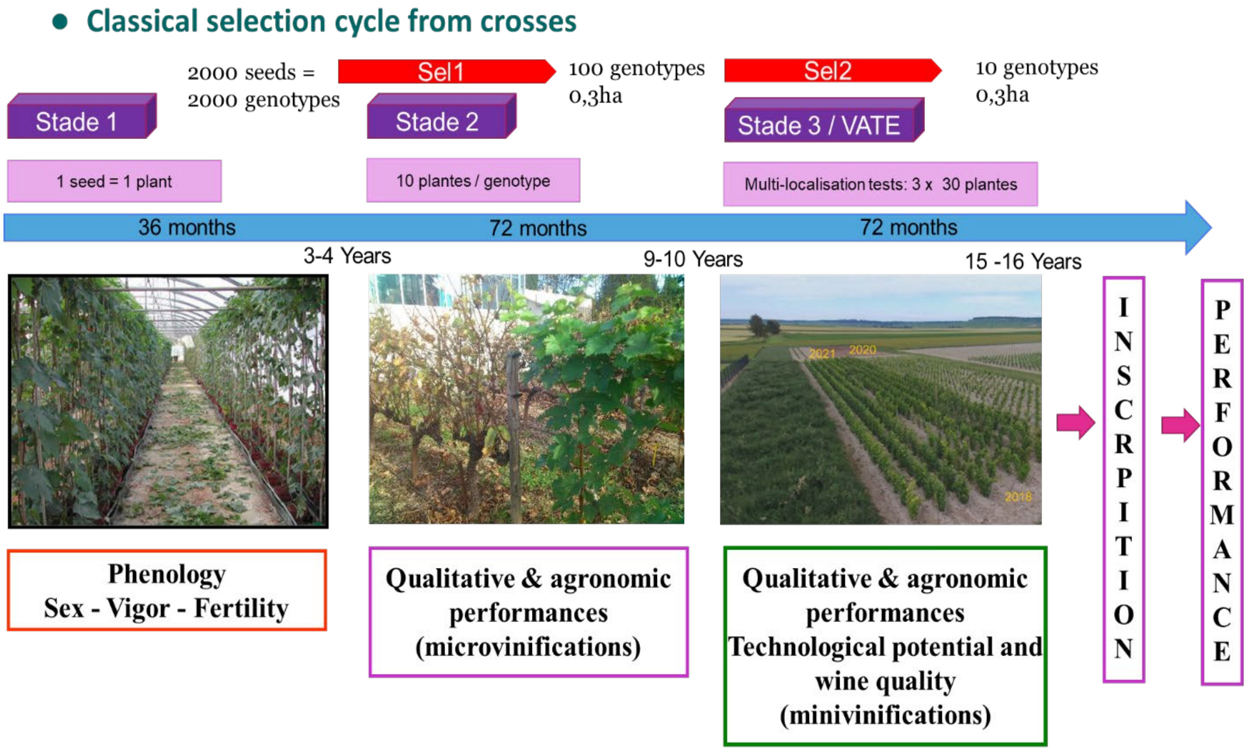
Variety regulation and fees in France

In terms of actual regulation towards commercialization, there are two layers in the regulation of new varieties in France for traditional breeding techniques. There is the “Catalogue” step (French for Catalog) which defines varieties which can reproduced and propagated into fields (presumably before commercialization) and then there is “Classement,” step which establishes varieties which can be used for commercial production of wine. These are French-specific regulatory elements on top of the EU regulatory element regarding varieties which can be used for production of wine. Some elements are established parallelly in the national and EU systems, such as the Catalog, which exists in both EU and French systems. At the EU level, only propagating material of vine varieties listed in the EU Catalog of at least one member state can be marketed on the territory of the EU.

The Catalogue has evolved and expanded in recent years to address disease and drought resistance varieties. The process of testing and approval involves fees, tests, and time is lengthy.

French registration fees are low to negligible compared to cost figures mentioned in Lassoued et al. and AgBioInvestor (2022). Testing takes time but is not expensive (€850in the first year of testing, and €1700 in years 4 and 5 years, 5 years total). The various tests are also “inexpensive” (less than €1000 each). Hence, the significant costs are duration for testing and delays, the provision of various documentation and forms, and research staff time involved. The fee structure is as follows: Droit administratif unique : €660, Droit réduit examen DHS (Distinction Homogénéité Stabilité): €320. Fees DHS for 1st year €850, subsequent observation years (€1700 in years 4 & 5). For varieties already registered elsewhere in the EU or for a traditional variety already referenced, the fees are €330 for administrative fees and €850 for the technical evaluation. There are also modest annual fees to maintain the registration of the variety. All these would take place for any innovation, either conventional hybrid or based on biotechnology.

FranceAgriMer is the French organism in charge of controlling production and distribution of these new material elements (seeds and plants). Registration in the French catalog is decided by the Ministry of Agriculture from proposals made by the Permanent Technical Selection Committee (CTPS in French). These proposals are made on the basis of studies conducted within the framework of the CTPS managed by GEVES (Groupe d'Etude et de contrôle des Variétés Et des Semences), the institution in charge of evaluating new varieties. GEVES collaborates with the EU CPVO which would streamline the process of an EU approval.



- Classical selection cycle from crosses

Stade 1

1 seed = 1 plant

2000 seeds =
2000 genotypes

Sel1

Stade 2

10 plantes / genotype

100 genotypes
0,3ha

Sel2

Stade 3 / VATE

Multi-localisation tests: 3 x 30 plantes

10 genotypes
0,3ha

36 months — 72 months — 72 months

3-4 Years

9-10 Years

15 -16 Years

Phenology
Sex - Vigor - Fertility

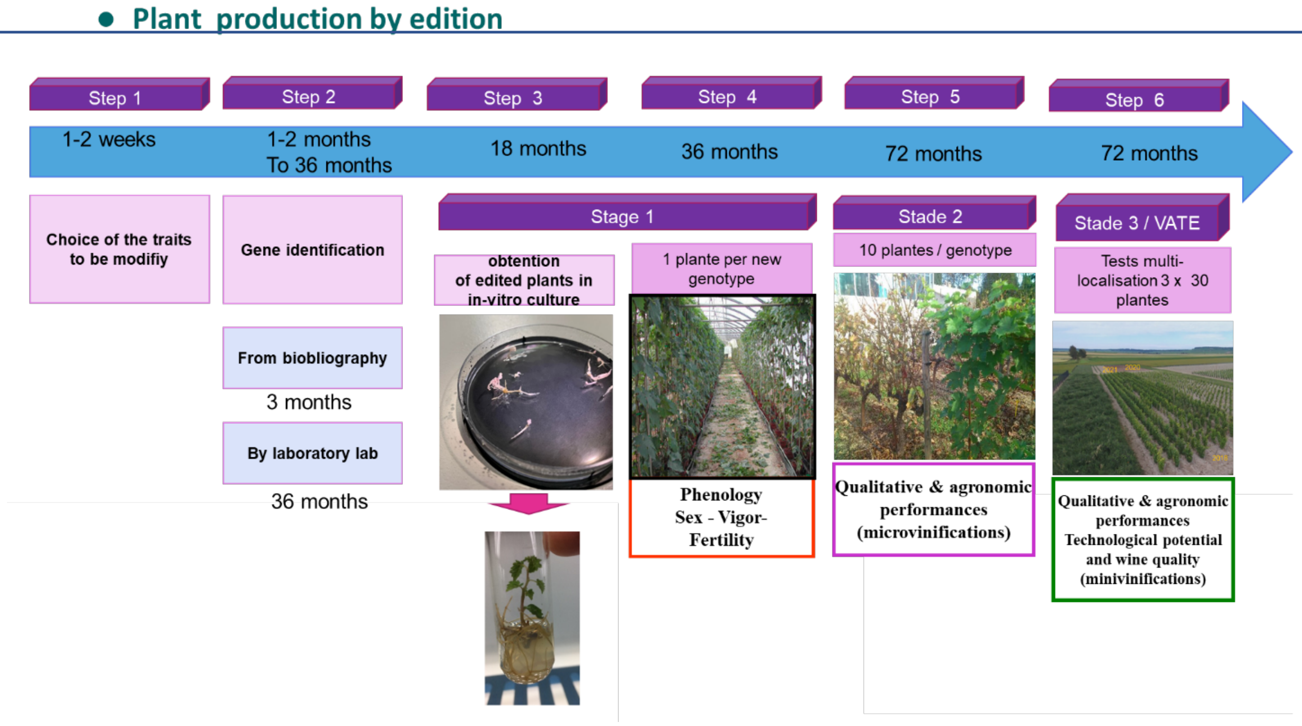
Qualitative & agronomic performances
(microvinifications)

Qualitative & agronomic performances
Technological potential and wine quality
(minivinifications)

INSCRIPTION

PERFORMANCE

Appendix Figure 2. Conventional-hybrid breeding. Source: This (2022)



- Plant production by edition

Step 1 — 1-2 weeks

Step 2 — 1-2 months
To 36 months

Step 3 — 18 months

Step 4 — 36 months

Step 5 — 72 months

Step 6 — 72 months

Choice of the traits to be modifiy

Gene identification

From biobliography

3 months

By laboratory lab

36 months

Stage 1

obtention
of edited plants in
in-vitro culture

1 plante per new genotype

Phenology
Sex - Vigor-
Fertility

Stade 2

10 plantes / genotype

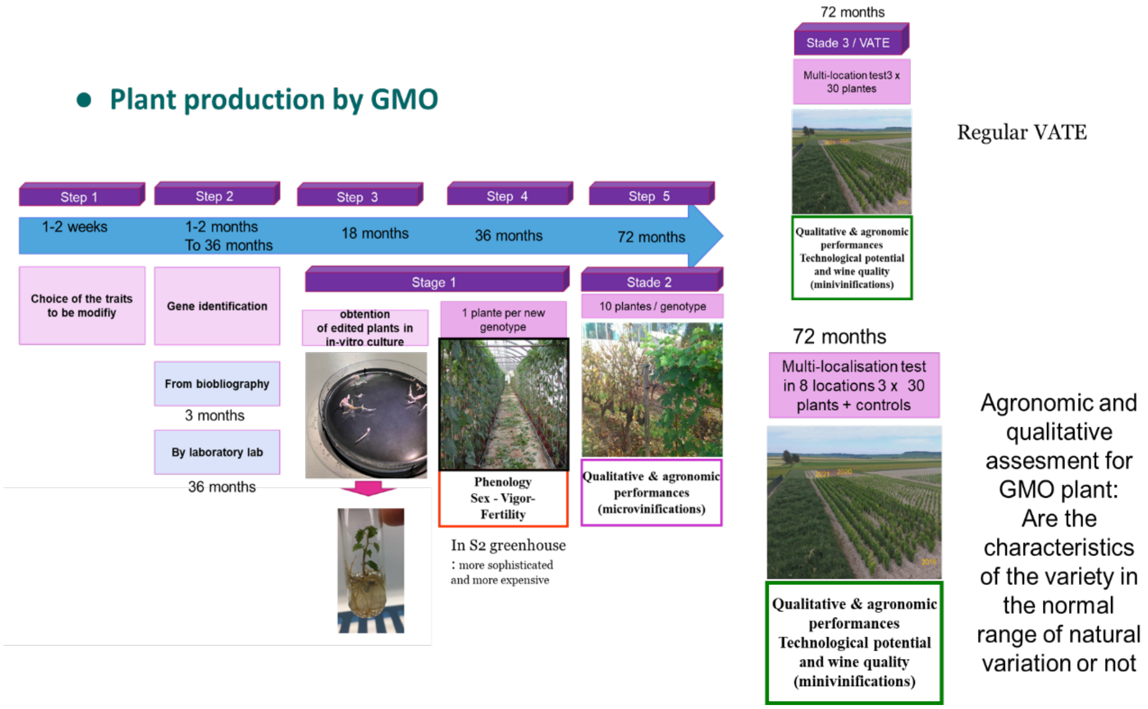
Qualitative & agronomic
performances
(microvinifications)

Stade 3 / VATE

Tests multi-localisation 3 x 30 plantes

Qualitative & agronomic performances
Technological potential and wine quality
(minivinifications)

Appendix Figure 3. GenEd breeding steps. Source: This (2022)



- Plant production by GMO

Step 1
1-2 weeks
Choice of the traits to be modifiy

Step 2
1-2 months
To 36 months
Gene identification
From biobliography
3 months
By laboratory lab
36 months

Step 3
18 months

Step 4
36 months

Step 5
72 months

Stage 1
obtention of edited plants in in-vitro culture
1 plante per new genotype
Phenology
Sex - Vigor-
Fertility
In S2 greenhouse
: more sophisticated
and more expensive

Stade 2
10 plantes / genotype
Qualitative & agronomic performances (microvinifications)

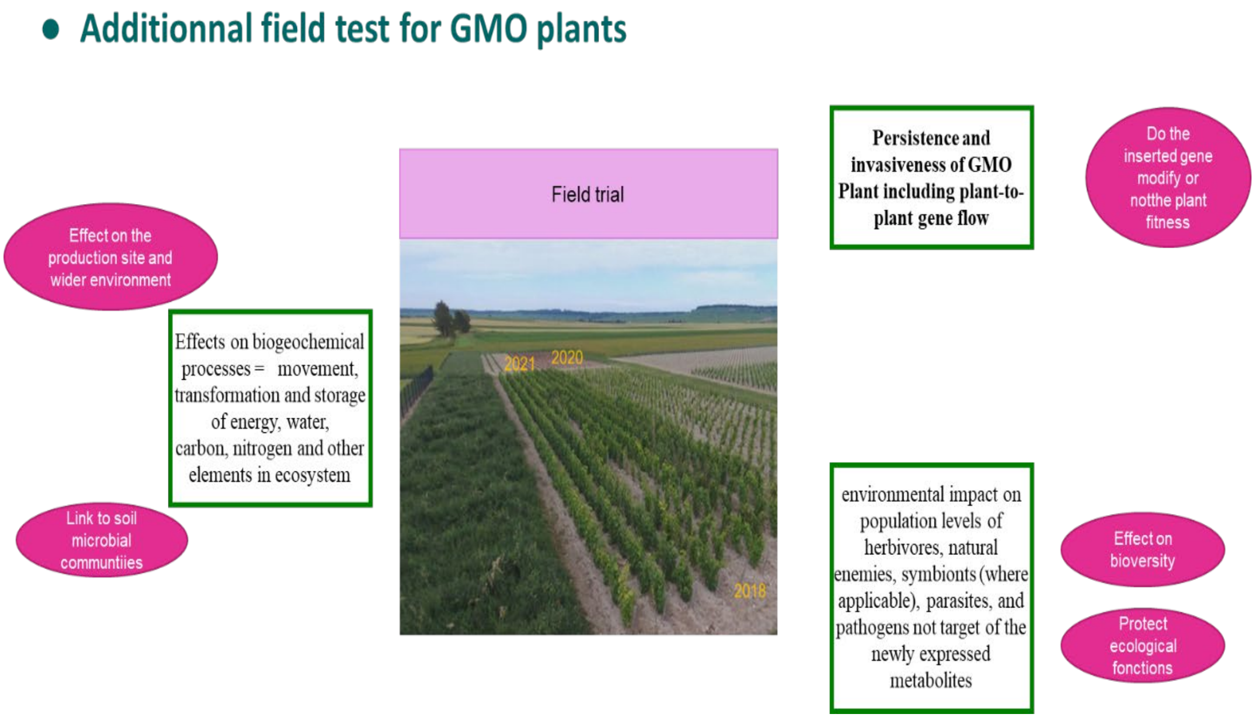
72 months
Stade 3 / VATE
Multi-location test3 x 30 plantes
Qualitative & agronomic performances
Technological potential and wine quality (minivinifications)

Regular VATE

72 months
Multi-localisation test in 8 locations 3 x 30 plants + controls
Qualitative & agronomic performances
Technological potential and wine quality (minivinifications)

Agronomic and qualitative assesment for GMO plant: Are the characteristics of the variety in the normal range of natural variation or not

Appendix Figure 4. Comparison GenEd and GMO regulated innovation. Source: This (2022)



- Additionnal field test for GMO plants

Effect on the production site and wider environment

Effects on biogeochemical processes = movement, transformation and storage of energy, water, carbon, nitrogen and other elements in ecosystem

Link to soil microbial communtiies

Field trial

Persistence and invasiveness of GMO Plant including plant-to-plant gene flow

Do the inserted gene modify or notthe plant fitness

environmental impact on population levels of herbivores, natural enemies, symbionts (where applicable), parasites, and pathogens not target of the newly expressed metabolites

Effect on bioversity

Protect ecological fonctions

Appendix Figure 5. Comparison GenEd and GMO regulated innovation (cont.). Source: This (2022)

Appendix 2 on EFSA duration of GMO approvals for food and feed uses in 2022-2023

Appendix 2 provides the regulatory time estimate for transgenic innovations to be approved in recent years. This appendix calculates recent delays and time periods required for the approval of a new GMO event by the EFSA in the last two years (2022 and 2023). 11 cases were found. The average approval time was 4.06 years for the 11 cases see Appendix Table 2. The estimate is rounded to 4 years. This recent average is slightly below that of Smart et al. (2017) of 4.83 years. The appendix provides the reference to these requests in the *EFSA Journal,* and their respective duration extracted from the text. Note that these time periods are for approvals for feed and food uses, not for planting/cultivating, which would require more scrutinizing and longer approvals. There are no grape cases unfortunately among the 11 cases identified. The EFSA delay is then integrated in the cost of delay framework explained in the manuscript.

1. EFSA Panel on Genetically Modified Organisms (GMO Panel). Assessment of genetically modified maizeBt11 x MIR162 x MIR604 x MON 89034 x 5307 x GA21and 30 subcombinations, for food and feed uses, under Regulation (EC) No 1829/2003(application EFSA-GMO-DE-2018-149). *EFSA Journal* 2023 21(6): 8011. (5 years April 2018-2023)
2. --------------------------------. Assessment of genetically modified cotton COT102 for food and feed uses, under Regulation (EC) No 1829/2003(application EFSA-GMO-DE-2017-141) *EFSA Journal* 2023 21(6): 8031. (April 2017-May 2023, 6 years+)
3. -------------------------------. Assessment of genetically modified maize GA21 × T25 for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-DE-2016-137*). EFSA Journal* 2023 21(1):7729. (Nov 2016 to November 2022 6 years).
4. -------------------------------. Assessment of genetically modified maize MON 87419 for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-NL-2017-140). *EFSA Journal* 2023 21(1):7730 (April 2017 to 2022 Nov, 5years and 8 months).
5. -------------------------------. Assessment of genetically modified Maize MON 87429 for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-NL-2019-161). *EFSA Journal* 2022 20(11):7589. (end of September 2022- Oct 2, 2019, 3 years). Note no production.
6. -----------------------------------. Assessment of genetically modified maize MON 95379 for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-NL-2020-170). *EFSA Journal* 2022 20(11):7588. (end of September 2022 – end of November 2020, 1Y 10 months or 22 months).
7. ------------------------------------. Assessment of genetically modified maize DP4114 × MON 89034 × MON 87411 × DAS-40278-9 and subcombinations, for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA GMO-NL-2020-171) *EFSA Journal* 2022 20(11):7619 (end of September 2022-11 December 2020 or 1 y 9 month or 21 months).
8. ----------------------------------. Assessment of genetically modified maize MON

9034 × 1507 × MIR162 × NK603 × DAS-40278-9 for food and feed uses, under regulation (EC) No 1829/2003 (application EFSA-GMO-NL-2018-151). *EFSA Journal* 2022 20(8):7451. (May 2018-July 2022 or 4Years 1 month or 49 months)

9. --------------------------------------. Assessment of genetically modified oilseed rape MON 94100 for food and feed uses, under regulation (EC) No 1829/2003 (application EFSA-GMO-NL-2020-169). *EFSA Journal* 2022 20(7):7411. (20 June 2022- Nov 16, 2020, or 1year 7 months or 19 months).

10. ---------------------------------------. Assessment of genetically modified maize DP4114 × MON 810 × MIR604 × NK603 and subcombinations, for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-NL-2018-150). *EFSA Journal* 2022 20(3):7134. (26 January 2022-May 8, 2018, or 3years 8 months or 44 months).

11. ------------------------------------. Assessment of genetically modified maize GA21 × T25 for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-DE-2016-137). *EFSA Journal* 2023 21(1):7729. 30 (end of November 2022 – 14 Nov 2016, or 6 years)

Appendix Table 2. Required times for EFSA approvals 2022-23

1	60
2	73
3	72
4	68
5	36
6	22
7	21
8	49
9	19
10	44
11	72
Average rounded in years	4.06