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REPORT FROM THE COMMISSION

Experience of Member States with Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms for the period 2014 – 2018

{SWD(2021) 114 final}

REPORT FROM THE COMMISSION

Experience of Member States with Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms for the period 2014 – 2018

The information contained in this document has been compiled by the Commission from individual reports submitted by Member States in accordance with Article 17 of Directive 2009/41/EC of the European Parliament and of the Council[1] on the contained use of genetically modified micro-organisms.

INTRODUCTION

Directive 2009/41/EC (hereinafter referred to as "the Directive") provides that every three years Member States send to the Commission a summary report on their experience with the Directive[2] and that the Commission publish a summary based on these reports[3]. The Commission has already published four reports pursuant to that directive or to the preceding Council Directive 90/219/EEC[4], for the periods 1999-2003, 2003-2006, 2006-2009 and 2009-2014[5].

The present report covers the period from June 2014 to December 2018. Two rounds of consultation of Member States were performed:

1. A first consultation (run in the first quarter of 2018) to cover the period June 2014 – December 2017: all Member States sent individual reports, based on a common questionnaire providing information on:

- General implementation of the Directive;
- Overview of the contained uses and premises for GMMs[6];
- Notification, authorisation and administration of investigational medicinal products that contain or consist of GMOs;
- Notifications and measures for gene drive modified organisms.

2. An additional consultation (run in the first quarter of 2019) for the period January – December 2018 was performed, with an updated version of the questionnaire, to receive information regarding notifications of contained uses of GMMs/GMOs produced with new mutagenesis techniques and regarding the impact of the ruling of

[1] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (OJ L 125, 21.5.2009, p. 75)
[2] Article 17(2)
[3] Article 17(3)
[4] Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms (OJ L, 117, 8.5.1990, p. 1)
[5] The reports are available on this European Commission webpage.
[6] And for GM animals/GM plants if also covered under national contained use legislation

the Court of Justice of the European Union (CJEU) of 25 July 2018 in Case C-528/16[7].

For the year 2018, 25 Member States submitted their individual reports[8]. Croatia provided a statement on the "Directive 2009/41/EC and new mutagenesis techniques". Therefore, Croatia contribution for the year 2018 is only referred to in the part related to new mutagenesis techniques. In addition, Spain and the Netherlands referred in some part of their replies to the questionnaire, to comments provided as a follow-up of the Standing Committee on GM food and feed (September 2018), and the Regulatory Committee under Directive 2001/18 (October 2018) where competent authorities were requested to provide information relevant to the implementation of the Court ruling.

The following text summarises the information given by the Member States under the headings provided and highlights similarities and differences between the experiences of the Member States. Furthermore, it provides the Commission's views on some questions raised by Member States regarding the implementation of the Directive, notably as regards the scope of the Directive and the relevance of the Court ruling in Case C-528/16.

Further details from the individual Member States' reports are provided in the accompanying Commission Staff Working Document.

It should be noted that while the Directive provides for "*common measures for the evaluation and reduction of the potential risks arising in the course of all operations involving the contained use of GMMs and to set appropriate conditions of use*" (Recital 8), the implementation of the Directive is the responsibility of Member States. In particular, Member States when transposing the Directive into their national legislation could for example decide to implement more stringent requirements, in accordance with Article 193 TFEU. Member States may also apply the principles of the Directive to GM animals and GM plants, as it is currently not regulated under Union legislation.

The Commission organises regular meetings of the national competent authorities responsible for the Directive, where discussion on topics of common interest between Member States are discussed.

Disclaimer: The information contained in this report relating to Member States is based on Member States' individual reports.

Neither the European Commission nor any person acting on its behalf is responsible for the content of that information and of any use made of it.

Clarifications provided in the report addressing questions by Member States reflect the views of the European Commission. However only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

[7] Judgment of 25 July 2018, Case C-528/16, *Confédération paysanne and Others v. Premier ministre and Ministre de l'agriculture, de l'agroalimentaire et de la forêt* (ECLI:EU:C:2018:583)
[8] Croatia, Italy and Poland did not sent individual reports.

PART I: GENERAL IMPLEMENTATION OF THE DIRECTIVE

1. Notification and approval systems (and relevant changes)

1.1 Approval systems

As reported previously, national systems differ slightly in terms of authorities involved. Only Latvia reported a change[9] in the involved competent authority, as compared to the previous reporting period.

In many Member States (Belgium, Bulgaria, the Czech Republic[10], Denmark[11], Ireland, Greece, Spain[12], Latvia, Lithuania, Malta, the Netherlands, Poland, Portugal, Romania, Slovenia, Slovakia,), the competent authorities for the Directive were the Ministry of Environment or Agencies focusing on environmental issues. In case of GMO, Food and Veterinary authorities/directorates are also involved (Portugal, Slovenia[13]).

In other Member States, the tasks of the competent authority were carried out by other Ministries, such as the Ministry of Health (Croatia[14], Italy, Luxembourg and the United Kingdom), the Ministry of Labour (Estonia, Cyprus and Austria[15]), the Ministry of Education and Research (France[16] and Austria[17]), the Ministry of Agriculture (Hungary[18]), or specific authorities for Biotechnology/Biosafety (Finland[19]), Food Safety and Consumer Protection (Germany) or Work Environment (Sweden[20]).

In many Member States, the competent authority is assisted by advisory scientific bodies in the risk assessment/authorisation process[21].

In some Member States, the implementation is done by competent authorities at regional level (Belgium, Germany, Spain[22] and the United Kingdom), possibly further coordinated at national level (Belgium, Germany). In addition, in some Member States, the competent

[9] From Ministry of Agriculture to Ministry of Environment.
[10] In close collaboration with the Ministry of Health and the Ministry of Agriculture.
[11] Together with the working environment authority.
[12] In association with the Inter-ministerial Council for GMOs (CIOMG), which delivers the authorisation, for the contained uses carried out by Government Public Research Institutes or for activities with GMOs focused on medical purposes (clinical trials, human and animal medicines/vaccines, etc).
[13] For GM animals, registration of the premises involves the Veterinary authority, which operates under the Ministry of agriculture, food and forestry.
[14] Together with the Ministry of Science and Education.
[15] For contained uses other than those in Universities and scientific institutions.
[16] Or Ministry of Defense for establishments under its authority.
[17] For contained uses in Universities and scientific institutions.
[18] Together with the National Institute of Pharmacy and Nutrition.
[19] Together with the National Supervisory Authority for Welfare and Health, as supervisory authority.
[20] For contained use of GMMs. The Swedish Agency for Marine and Water Management is involved in case of contained use of water living GMO; for other contained uses, it is the Swedish Board of Agriculture.
[21] For example, Czech Commission for the Use of GMOs and Genetic Products; High Council for Biotechnology in France; Biotechnology Health Technical Committee in Italy; Commission on Genetic Modification (COGEM) in the Netherlands; Directorate General of Health and National Health Institute Doutor Ricardo Jorge in Portugal; Biosafety Commission, and various authorities according to the type of use in Romania; National Commission on Biosafety (CNB) in Spain, the Central Committee on Biosafety (ZKBS) in Germany.
[22] For other activities than those carried out by Government Public Research Institutes or activities with GMOs focused on medical purposes.

authority varies according to the type of use (Spain, Sweden) or the type of premises (France, Austria).

In many Member States, the competent authority for Directive 2009/41/EC is also the competent authority for Directive 2001/18/EC on deliberate release into the environment of GMO, while for 10 Member States[23] it is a distinct competent authority.

The vast majority of Member States have extended the scope of their transposing legislation to the contained use of GM plants and GM animals. This is usually because the national legislation covers all types of GM organisms: GMMs, GM plants and GM animals[24]. Some Member States[25] extended the scope of their transposing legislation specifically to require notification, risk assessment, enforcement and appropriate containment measures for contained use activities with GM plants and GM animals. Finally, Member States also referred to historical and political reasons (Denmark) and societal reasons (France), for such extension of the scope.

To note, Bulgaria uses a different classification for GM plants and animals, with only two classes[26], and Lithuania indicated that it will prepare specific requirements for the contained use of GM plants and GM animals.

For the seven Member States[27] that have not extended the scope of their transposing legislation, the reasons were diverse. While in general the transposition followed the scope of the Directive and its definition of GMM, in Cyprus, an extension of the scope was not needed because there are no activities and/or installations involving GMOs.

Four Member States (the Czech Republic, the Netherlands, Portugal and Slovenia) reported a change in the notification and approval system compared to the last reporting period (2009-2014).

The Czech legislation is stricter than the Directive for Class 1 contained uses[28]. According to the amendment (which came into force on 1st January 2017), when carried out in a previously notified Class 1 premises, the user has to submit a notification but can already start the activity. The competent authority assesses the notification and may require additional information from the notifier and/or decide that the contained use has to be suspended.

The Czech Republic and the Netherlands also declared that new notifications formats (harmonised tables for the risk assessment, presentation of the data) and reporting systems have been put in place. This enhanced clarity for the notifiers and the competent authorities, which further ease the reviewing by the competent authority.

The new Portuguese law clarified the legal framework for the contained use of GM plants and GM animals, set a deadline to the consulted entities for issuing opinions and introduced the obligation for notifiers to report annually on contained uses of GMMs and GMOs.

[23] BE, CY, DE, EE, EL, FR, HR, IT, SE and UK.
[24] BE, BG, DE, DK, ES, FR, NL, AT, PT, SI, FI and UK.
[25] BE, BG, CZ, IE, HR, HU, PL, SK and UK.
[26] Class A: no or negligible risk for the human or animal health and for the environment; class B: all other cases.
[27] EE, EL, IT, LV, LU, CY and RO.
[28] Until the end of 2016, a new notification was already required for each new activity carried out in a previously notified Class 1 premises.

Slovenia reported a change in the administrative procedures (some costs to be covered by the notifier in specific cases).

1.2 Notification process

During this period, most Member States processed the notifications[29] within the statutory timeframe[30], while 11 Member States[31] declared delays (usually for less than 15% of the assessed notifications[32]). Greece and Latvia reported that there were no notifications submitted during this period, and Luxembourg, which has an authorisation procedure in place, does not apply any notification process.

When delays occurred, they were mostly due to some peaks in the number of notifications submitted (Germany and France), insufficient staff resources compared to the workload in the competent authority (Germany) or the consulted scientific bodies, or change of the Committee members (Croatia, Italy, Slovenia and Sweden). Furthermore, Italy reported to have no effective IT tools to archive and retrieve all the information provided by the users.
Waiting for additional information from the notifier after a request by the competent authority is also causing delays (Belgium, France, Italy and Sweden). However, in Belgium and Spain, which both include an on-site visit in their assessment, the timeframe for the notification assessment can be suspended if the competent authority is waiting for complementary information from the users.

Administrative issues linked to consulted scientific bodies or other authorities (Germany, Italy, Slovenia, Slovakia and the United Kingdom) were also causing delays. Slovakia considers that the time during which the competent authority is waiting for the opinion of its advisory body should not be taken into account.

In Belgium, different procedures apply according to the regions, and in the Flemish Region there are two authorisations processes with different timeframes which are linked (authorisation for the contained use, 45 or 90 days; environmental permit, up to 6 months), possibly impacting the contained use authorisation as it can be given only after the environmental permit is granted. The Netherlands had also delays due to the implementation of the new rules of the revised GMO Decree.

Finally, Germany, the Netherlands and Slovakia highlighted that the increasing complexity of the notifications makes the processing time longer.

Member States were taking measures to reduce or prevent delays in processing notifications (unless those delays were unusual and unlikely to be repeated, like in the United Kingdom).
For example, France adjusted the resources to the amount of notifications received and Luxembourg to perform field inspections.

[29] "Notification": the presentation of the requisite information to the competent authorities of a Member State.
[30] Articles 8(2), (3) and 9(2) of the Directive.
[31] BE, DE, IE, FR, HR, HU, IT, NL, SI, SE and UK.
[32] With the exception of two Member States, which reported 50% of notifications processed with delay (Slovenia in the period of 2014-2017, France for the year 2018).

Member States are also improving the communication between the different parties involved: between the notifiers and the competent authority (including consultation prior to submission in Hungary, tracking of notifications with a unique notification number in Sweden); between the competent authority and the consulted scientific body. For example, in Italy efforts are being made to provide a web platform to the competent authority and the scientific board members to share the notifications electronically and to obtain signed opinions by each member of the scientific board. Finally, users and authorities also adjusted to new practices when introduced (the Netherlands).

Regarding the notification process in general, half of the Member States[33] that received notifications do not encounter specific difficulties.

In addition to previous comments, some Member States further reported difficulties related to the quality and completeness of the submitted notifications (the Czech Republic, Denmark Germany, Finland and Sweden). Moreover, notifiers can face issues to interpret some terms of the national legislation (case of the Flemish region of Belgium, where the user can submit a 'notification' or an 'admission request' for subsequent class 2 contained uses). On the other hand, in the United Kingdom, the users understand well the notifications requirements and the notification process is working well.

Denmark and Finland noticed administrative burden related to the mobility of researchers between institutions, leading for example to repeated new notifications by the same notifier of different premises, or to the lack of correct notifications for new uses. It also happens that when the premises is no longer used, the notifier forgets to inform the competent authority, or that after renovation of an old premises, the renovated structure does not correspond anymore to what had been notified.

France and Italy also reported difficulties related to IT tools. Italy mentioned the lack of an electronic system that would allow the notifier to submit and update its notification electronically, while France underlined that the IT tool used needs further development to fulfil all the needs.

More generally, Member States reported issues for notifications linked to the definitions of the Directive and the classification of the contained uses (see paragraph 6 Interpretation and implementation of the Directive, p. 12).

To help improving the content of the notifications, some Member States[34] suggested providing guidance and clarification on the notification requirements to the users, for example on the competent authority webpage or in guideline documents, or by providing consulting to the users. Better information and explanation provided to the consulted bodies involved in the assessment of the notifications was also mentioned.

New IT tools or templates were/could also be developed[35], together with improving the administrative procedures for more efficiency, and streamlining the practices.[36] Sweden and

[33] CZ, EE, HR, CY, LT, HU, MT, AT, PL, PT, RO, SI, UK.
[34] BE, DK, DE, EE, IE, SI, FI.
[35] CZ, ES, FR, IT, NL.
[36] FR, NL.

the Czech Republic reported that the changes done in their legislation contributed to ease and speed up the notification process.

Aspects specifically related to clinical trials, and interpretation of the definitions of the Directive in relation with new genomic techniques are discussed in parts III (p. 20) and IV (p. 24) respectively.

2. Waste disposal

In general, Member States[37] declare that waste is managed by class of contained use and type of waste, in accordance with the requirements of Article 5 and of Annex IV and Annex V of the Directive. Some Member States[38] prescribe that all types of waste (including from class 1) must be inactivated prior to disposal. For waste resulting from class 1 use, Denmark and the United Kingdom mention a risk assessment in each specific case, and Spain recommends inactivation. The Member States[39] that did not provide information on these aspects explained that there is no activity or no experience in this area.

In general, the users apply autoclaving and chemical inactivation to inactivate GM waste on site, and incinerate GM plants and animals. Other treatments to inactivate waste for different tissues of a GM-plant or animal can be used individually or combined (alkaline hydrolysis, UV treatments, freezing, mechanical treatments, composting). Other procedures are evaluated on a case-by-case basis and are subject to validation. For example, Germany authorised the inactivation of soil containing GMO-seeds by a validated steam method.

16 Member States[40] indicated that they have waste treatment facilities authorised to inactivate waste arising from contained use premises.

Many Member States[41] reported that if inactivation of waste from class 1 and 2 is not possible in situ, or in case of large volume of waste, it is transported in properly sealed and labelled containers to a dedicated authorised waste facility, by specialised transport companies (certified for collection of hazardous waste), and according to the rules for the transport of dangerous goods[42]. Transport and disposal are recorded (Germany, the United Kingdom). In addition, in some Member States (Spain, France, Malta, Romania and Slovakia) certified companies collect also inactivated waste.

Nine Member States[43] indicated that some waste from contained use activities is recycled after inactivation. The purposes of the recycled waste are compost, fertilizer and biogas. Finland noted that, as the concept of circular economy is gaining ground in the EU, the legislative issues on recycling large quantities of GMM waste or byproducts should be addressed.

[37] BG, CZ, DK, DE, ES, FR, HR, IT, CY, LU, AT, RO, SI, SK, FI and UK.
[38] BE, IE, LT, MT, NL, PT, SE.
[39] EL, LV.
[40] BE, DE, EE, IE, ES, FR, HR, LT, LU, HU, NL, RO, SK, FI, SE, UK.
[41] BE, DE, EE, IE, FR, HR, LU, NL, SK, FI, SE, UK.
[42] ADR, formally the European Agreement of 30 September 1957 concerning the International Carriage of Dangerous Goods by Road.
[43] BE, CZ (only in the period 2014-2017), DK, DE, LT (only in 2018), HU (only in 2018), SI, SK and FI.

3. Inspection and enforcement issues

The control procedures put in place by the Member States included regular inspections according to set criteria (class of risk, periodicity, etc.), ad hoc unannounced inspections, and audits of premises approved for the first time. The inspections evaluated the compliance with the Directive, the correctness of the risk assessment classification, the effectiveness of the respective containment level, the labelling and transport of GMOs within the premises, the waste treatment, the training of the personnel, and the fulfilment of administrative obligations. In some cases, it included also sampling of materials. Ireland reported using a checklist originally adopted by the European Enforcement Project (EEP) on Genetically Modified Organisms[44] during its inspections.

In some Member States, inspections were conducted by specialised inspectors from the competent authority, while in others, inspections were carried out at the request of the competent authorities by specialised inspectors from other ministries or services. In some Member States, controls are carried out by regional authorities. Some Member States developed documentation or training for inspectors: Italy developed a training course for inspectors, Portugal established a guide to support the inspections, and Luxembourg designed a new inspection checklist and procedure.

The number of inspections carried out during the reporting period varies among Member States, from 10 to 100% of the premises controlled. Few countries[45] did not carry out any inspection during the reporting period, mostly because no contained use premises/activities were notified.

In many countries[46], the inspections gave priority to premises of higher class of contained use, and to new premises/activities. The frequency of inspection varies according to the class of use: for countries with premises for class 4 uses, those are usually inspected annually. The frequency for class 3 premises varies between once per year to once every 3 or 5 years. In general, class 1 and class 2 premises are inspected at a lower frequency than class 3-4 premises, and in some countries those are controlled remotely, or they are not controlled as part of a proactive inspection programme. Inspections can also be triggered in case of incidents or accidents, to verify the implementation of corrective measures. Finally, unscheduled inspections may take place when unauthorised use of GMO is suspected (Bulgaria).

During inspections, some contained uses of GMOs/GMMs with no correct authorisation (not notified), or with incorrect classification of the contained use, were found, possibly leading to insufficient containment measures. A minority of Member States did not encounter issues during inspections[47].

[44] The European Enforcement Project on GMOs (EEP) is a network of regulators from inspectorates across the European Union (and beyond) responsible for the inspection of activities involving GMOs. The network was founded in 1997.
[45] IT, EL, LV, MT, PT.
[46] BE (Brussels-Capital Region), DE, IE, NL, FI, SE, UK.
[47] BG, HR, CY, LT.

Among the issues reported, it happened that procedures described in the notifications, or laboratory installations, did not correspond to the laboratory practice/reality. Other reported issues concerned deficiencies in good laboratory practices (GLP) affecting the premises (e.g organisation, inadequate or deficiencies in laboratory equipment, incorrect labelling of the laboratory and equipment), the users (e.g inadequate protective clothing, missing instructions, insufficient training) or the administrative procedures (e.g lack of complete, up-to date, accurate documentation, incomplete recording of staff working in the premises). Further issues related to the lack of appropriate procedures for inactivation of the GMMs and waste management, as well as insufficient biosafety measures (e.g no restricted access to the premises where the contained use takes place, insufficient hygiene and disinfection methods). Various countries reported a lack of internal control procedures (e.g. biosafety officer in charge of implementing properly the confined and control measures according to the class of risk). Finally, administrative issues (delayed notification of changes in responsible persons, missing recording of staff training, missing notification that a premises is no longer used for contained uses) were also found.

In terms of enforcement, when inspections identified situations requiring corrective actions, the competent authorities declare to have used a number of instruments (inspection reports, letters, warnings, fines, etc.) to ensure remedial action and compliance from the users within a set timeframe.

If the non-compliance issues could result in increased risk for human or animal health or for the environment, all activities involving GMOs would be immediately stopped and the GMOs destroyed. For minor issues (e.g. regarding documentation), the deficiencies were corrected at the time of the inspection. In general, users implemented the corrective actions requested by the authorities in the given timeframe, and competent authorities controlled this with follow-up inspections, or by checking the updated documentation (including pictures).

In case of contained use or premises not notified, the user had to submit the appropriate notification, and in Slovakia, the competent authority imposes a fine to the user and publishes the corresponding decision online.

If issues were detected before the start of the contained use, users had to correct the deficiencies before beginning the activities. In some cases, the competent authority would also add conditions in its approval decision for the notified contained use. On the other hand, Finland reported a case were more information was asked regarding a contained use, which was not notified appropriately and already finished, to assess the risks a posteriori.

In order to minimise the occurrence of those issues, users provided more adequate protective equipment to the laboratory staff, as well as more information and training, including to the biosafety officers and with the staff in charge of waste management and maintenance of the infrastructures. In some cases, the users nominated a dedicated person for dealing with legal and safety requirements, internal controls, and liaising with the competent authorities. The communication between users and competent authorities can also be reinforced: in some Member States, the user asks questions to its competent authority prior to the notification, to get clarifications on the requirements and information about actions to be carried out.

Some competent authorities also make recommendations, and disseminate various checklists, guidelines, best practices and methodology documents to the users. Some also organised regular informative sessions, consultations with users, to raise awareness on biosafety before

approval of the contained uses. They also organised specific trainings about the legal requirements for GMMs/GMOs uses for the biosafety officers, and emphasised the importance of internal control procedures. The inspection visits are also used to discuss about plans for future contained uses where the users can get advices.

Regarding the case of premises not used anymore, for which it happens that the user forgets to inform its competent authority, in Slovenia, the competent authority specifically explains to the user, at the time the premises is notified, the conditions for a future deletion of the installation from the register of contained use premises.

4. Accidents

Very few Member States (Belgium, Germany, Finland and the United Kingdom) reported accidents[48], or some incidents (the Netherlands).

Belgium reported one accident in Wallonia due to a technical failure. An external expert analysed the corrective measures taken and the internal contingency plan, and gave advice on additional measures that should be taken.

Germany reported four accidents, two due to a technical failure (water leak in a class 3 premises, malfunction of a fermenter with a discharge of a large amount of GMM class 1 cell culture), one because of incorrect installation, and one related to the infection of a laboratory staff member. The competent authority was informed and corrective actions were taken by the users. In some cases, the user and the authorities informed also the public. The competent authority granted a permission to resume work only after completion of further actions by the user and performed follow-up inspections.

Finland reported few needle stick accidents concerning employees working with GMMs, and also a case of an effluent overflow in a class 1 premises. In the latter case, technical improvements of the installation were done, as well as training of the staff to recognise and prevent similar situations in the future. The competent authority examines each case and decides whether these measures are sufficient, and the inspection services supervise that the corrective measures are actually implemented.

The United Kingdom reported one accident, involving a person infected via needle stick while working in a class 2 laboratory, preparing GM non-replicative oncogenic Lister vaccinia virus. The competent authority carried out a full investigation of the causes of the accident, which included an inadequate risk assessment for procedures and inadequate training for the use of sharps with GM biological agents, inadequate accident and emergency procedures, and failure to notify relevant people in a timely manner, and informed the Commission. Various measures were put in place to prevent such type of accident, including training for all staff involved in GM work, review of the risk assessments for GMOs, establishment of formal emergency procedures, and formalisation of the role of occupational health in accident and emergencies.

[48] According to the Directive, "accident" means any incident involving a significant and unintended release of GMMs in the course of their contained use which could present an immediate or delayed hazard to human health or the environment.

The Netherlands reported several incidents due to needle stick injury. Usually the laboratory staff members were prescribed a curative medication, as a precautionary measure. There were also some incidents related to incorrect waste management, to technical failures or to the use of ineffective disinfectant, leading to the possible accidental release of small amount of GMO material (class 1 or class 2). Some of the incidents occurred during construction or renovation activities. There was also a case of maintenance work, which caused a change from under-pressure to over-pressure in a class 3 unit not yet in use for experiments. In those reported cases, there was a follow-up between the biosafety officer and the competent authority. One case led to a follow-up extensive inspection. It was required that technical measures, better procedures and safer type of needles were put in place/used to prevent similar incidents. Maintenance work was also followed by internal inspection by the biosafety officer before contained use activities were re-started.

The Commission notices a different perception of "accident" versus "incident" (which is not defined per se in the Directive) between Member States, and the classification of an event as "accident" is the responsibility of the competent authority, based on the risk for human health or the environment. In case of accident, the competent authority has to inform the Commission, according to article 15.1(b) of the Directive, and according to article 15.2 the Commission shares this information with other Member States.

5. Public consultation

While some Member States[49] do not carry out public consultations under their contained use legislation, the majority of them[50] organised public consultations when appropriate, according to Article 12 of the Directive.

The procedures for public consultation aim at providing general information to the public, or more specifically to the neighbourhood of the premises, regarding the contained use of GMMs and GMOs. The comments received from the public (usually in writing, but possibly through the organisation of public debates) are taken into account by the competent authority when taking its decision on a submitted notification. In some Member States, citizens have the possibility to file a complaint after the approval of the contained use.

Some Member States[51] focus the public consultations only on class 3 and/or 4 contained use notifications. In other Member States, the public consultation is carried out as part of the authorisation of the premises[52], under environmental permit procedures.

Usually, the information is made publicly available online. It contains a summary of the notification, and in some cases the risk assessment performed by the user, together with emergency plans. The information can also be published in national and/or regional newspapers. In some Member States, the information targets the neighbours of the contained use premises, with information displayed in the town hall, and at the premises.

In Ireland and Italy, it is the duty of the user to inform the public of the submitted notification, via publishing it in a (local) newspaper.

[49] CZ, EE, CY, LV, MT, AT, PT, FI, SE.
[50] BE, DK, DE, IE, ES, FR, HR, LT, LU, HU, NL, PL, RO, SI, SK, UK.
[51] DE, IE, ES, IT, SI.
[52] BE, NL.

In general, Members States reported that they did not receive responses to public consultations. In the Netherlands the received comments focused on the overall premises, and very rarely on the GMO aspects. In the United Kingdom, the responses to the consultations were predominantly supportive of the proposals (a summary is also published online). Only Belgium reported an observation received for a notification of a class 2 GMO contained use, concerning the proximity of the laboratory to houses and a school.

Finally, in several Member States, information on the premises for contained use of GMMs and GMOs is maintained updated and available online[53].

6. Interpretation and implementation of the Directive

While many Member States[54] reported no specific difficulties regarding the interpretation of the Directive, those that reported issues often refer to problems with the definition of GMMs/GMOs in the context of new genomic techniques, and synthetic biology, and whether a specific technique and the resulting organism fall within the scope of the Directive[55].

In general, this leads to situations where both the operators and competent authorities are uncertain whether a notification is actually required or not. In some cases, the competent authority had to decide on the application or not of the Directive.

6.1 New mutagenesis techniques

As explained in the introduction, the consultation of Member States was done in two phases: a first phase for the period 2014-2017, with replies submitted before the ruling of the CJEU of 25 July 2018 in case C-528/16 on new mutagenesis techniques. On that occasion, some Member States (Belgium, the Czech Republic, Germany, Ireland, Spain and the United Kingdom) considered that a harmonised legal interpretation at EU level on the regulatory status of GMOs obtained with new genomic techniques was urgently needed.

A second consultation phase of Member States covered the year 2018 (with replies provided in 2019). During that second consultation, questions related to interpretation and implementation of the Directive focused on notifications of contained uses of GMMs/GMOs produced with new mutagenesis techniques, and on the impact of the ruling for the competent authorities.

In the 2018 judgment, the Court ruled that organisms obtained by means of techniques/methods of mutagenesis constitute genetically modified organisms within the meaning of Article 2(2) of Directive 2001/18/EC, and that only organisms obtained by means of techniques/methods of mutagenesis which have conventionally been used in a number of applications and have a long safety record are excluded from the scope of that directive in accordance with Article 3(1) thereof.

In the Commission's view, the Court's interpretation of the exemption in Article 3(1) of Directive 2001/18, read in combination with Annex IB to that Directive as regards mutagenesis techniques, also applies to the exemption of mutagenesis techniques in Directive

[53] BG, LT, NL, PL, RO, SK, UK.
[54] EE, EL, FR, HR, CY, LV, LT, LU, MT, AT, PL, PT, RO, SI, SK, UK.
[55] BE, CZ, DE, IE, ES, HU, NL, FI, SE.

2009/41/EC. This conclusion is supported by various considerations, namely by the similarities between the two directives as regards their aim, the definitions of GMO/GMM and the construction of the exemption (i.e. by the combination of an Article formulated in similar terms in both directives and an Annex listing the exempted techniques); the fact that the predecessors of both directives (Directives 90/220/EEC and 90/219/EEC) also followed a similar approach as regards the scope of the exemptions; and, finally, the fact that the techniques exempted in Annex II, part A of Directive 2009/41 had a safety record at the time of the adoption of Directive 90/219/EC, which tends to confirm that the rationale for the exemption is the same in Directive 2009/41 as in Directive 2001/18.

From the above it can be concluded that microorganisms obtained by means of techniques/methods of mutagenesis which have not been conventionally used in a number of applications and do not have a long safety record are not exempted from Directive 2009/41/EC.

- Notifications of contained uses of GMMs/GMOs produced with new mutagenesis techniques

Various Member States indicated that they did not receive any notifications for GMMs/GMOs obtained with new mutagenesis techniques (Bulgaria, Denmark, Estonia, Greece, Cyprus, Latvia, Lithuania, Luxembourg, Malta, Hungary and Portugal). Germany indicated that a significant proportion of activities involving new mutagenesis techniques is not notified to the competent authority since no-risk or low-risk activities only need to be recorded by the researcher, not notified. Finland stated that specific details of the techniques used to produce the GMMs/GMOs are not notified to the competent authority. Other Member States (Ireland, Austria, Romania, and Slovakia) reported between 1 and 10 notifications for such GMMs/GMOs, including a commercial do-it-yourself kit. Belgium, the Czech Republic, Spain, France, Croatia[56], Slovenia, and the United Kingdom also received notifications, mostly for GMMs, and also for GM plants and GM animals (mice, xenopus). The United Kingdom estimates that among the 220 notifications received in 2018, half involve new mutagenesis techniques, while France reports a stable number of notifications over the past four years, with around 1000 requests per year.

Sweden considers unfortunate that the CRISPR-*Cas*-techniques are interpreted as only one type. They have several GMM uses involving CRISPR-*Cas* and gene editing, where both the *Cas*-gene and gRNA are provided by vectors in cells (or cells in laboratory animals). The purpose of those experiments is often to explore gene function, and the cell cultures or laboratory animals are only used for the purpose of such experiments. Hence, according to Sweden, there is no commercial aspect for not calling the experiments "contained use of GMM".

Bulgaria, the Czech Republic, Ireland, Spain, Croatia, and the Netherlands reported that they considered products obtained by new mutagenesis techniques as GMOs, in scope of EU legislation and of their national legislation, and assessed them as such (already before the Court ruling).

[56] Croatia did not submit its questionnaire for the year 2018, but provided a statement on the Directive and new mutagenesis techniques.

Sweden specified that it interprets "mutagenesis" as the well-known techniques with chemical or physical mutation methods, common at the time of the first Directive on contained use of GMM from 1990 (90/219/EEC[57]) and not the later methods involving nucleic acids and site specificity, but for Sweden, it is difficult to understand why some "new" methods should be included and why some should not.

In Germany, several but not all of the regional competent authorities have regulated genome-edited organisms as genetically modified organisms on a precautionary basis before the Court ruling. After the Court ruling, the regional competent authority concluded that - precautionary and unless otherwise stated - all organisms obtained using mutagenesis methods are to be regarded as GMOs, also within the meaning of the Directive on contained use. However, the Court ruling has brought more clarity to the debate, but it also poses challenges that still need to be resolved.

Some Member States indicated that they asked or will provide clarifications to users: the Hungarian competent authority requested users to report about all class 1 activities, including activities on new mutagenesis techniques, and informed them about the ruling and the necessity to submit notifications for class 2, 3 and 4 contained uses, if applicable. In the United Kingdom, the contained use guidance, which was last updated in 2014, will be updated to remove ambiguity relating to what may be considered as mutagenesis to bring it into line with the Court ruling.

- Impact of the Court ruling on new mutagenesis for the competent authorities

Some countries have no specific views on it (Denmark, Estonia, Cyprus, Malta, Romania and Sweden) and Portugal and Slovakia still need to evaluate it.

A number of countries indicate that it has no impact as risk assessment and management of contained uses of GMMs and GMOs obtained by new techniques are performed in the same way as other GMOs (Belgium, Germany, and the Netherlands). It is the same in Austria, which specified that all new mutagenesis techniques are fully covered by its national legislation (only non-directed mutagenesis is exempted). For the United Kingdom, little has changed regarding the Directive, since conventional mutagenesis continues to be exempted. There is also no impact for Greece, which did not receive any notification for contained use of GMMs. Latvia and Slovenia have so far no specific issues (new techniques not yet widely used in Latvia, while they are used in research laboratories in Slovenia and all activities are notified).

On the other hand, Bulgaria, Germany and Ireland mentioned difficulties in applying and enforcing the contained use legislation for GMOs obtained through new genomic techniques due to their detection and identification, and the difficulty to distinguish them from organisms obtained by classical mutagenesis or naturally. In the case of microorganisms, Bulgaria anticipates that additional difficulties will arise from the high natural variability of their genomes and the fast rates of evolution.

Regarding the detection of GMMs obtained through new genomic techniques, the Commission has mandated the European Union Reference Laboratory for Genetically

[57] Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms (OJ L 117, 8.5.1990, p. 1–14) – repealed.

Modified Food and Feed (EURL) to prepare together with the European Network of GMO Laboratories (ENGL), a report on the detection of genome edited microorganisms.

The Czech Republic and Spain noted a negative impact of the Court ruling on research, development and innovation. For Spain, the authorisation procedure of contained use activities involving the new genomic techniques will delay their implementation by EU researchers in comparision to those from other countries. This will reduce their competitiveness in terms of novelty in publications, technological transfer or patents. For the Czech Republic, projects aiming at developing gene edited crops are not realised because it would be practically impossible to place a new GMO on the EU market.

Finally, the Czech Republic and France noticed also an impact on administrative burden, respectively for the research scientists, and for the competent authority. France anticipates a 10- or 20-fold increase in number of notifications to be assessed and has not the adequate resources to assess those.

- Challenges

Some Member States pointed out some legal uncertainties about the application of the Directive in the light of the Court ruling.

First, Bulgaria, Ireland, Luxembourg and Finland, mention that the basis for applying the Court ruling to the Directive needs to be clarified since the Court based its decision on Directive 2001/18/EC. Bulgaria considers that the definition of GMMs in the Directive, and of GMOs in Directive 2001/18/EC are practically identical, so any conclusions related to the definition of GMO are likely be relevant with the necessary changes to the definition of GMM.

Bulgaria and Luxembourg underlined that the Directive does not have an equivalent to recital 17 of Directive 2001/18/EC, which excludes organisms obtained through certain techniques of genetic modification that have conventionally been used in a number of applications and have a long safety record. Therefore, for Luxembourg, clarification is needed whether organisms generated through the new mutagenesis techniques are to be considered subject to the contained use Directive or not.

In addition, Bulgaria stressed that there are significant differences in the conditions for exclusion of organisms from the scopes of each Directive. The exclusion criteria in Directive 2009/41/EC are broader and include self-cloning. In the light of the Court ruling, according to Bulgaria, it will seem enough that the criteria of Annex II part A are fulfilled to exclude a GMM from the scope of the Directive, without the necessity to demonstrate that the GMM is obtained by means of techniques/methods that have conventionally been used in a number of applications and have a long safety record. Under this interpretation, some GMMs obtained by gene editing might be considered to be the result of self-cloning and thus outside the scope of the Directive.

Germany is specifically asking if self-cloning using new molecular techniques (SDN3) continue to be exempted from regulation under the Directive. Luxembourg is wondering, if organisms that resemble those produced by self-cloning are outside the scope of the Directive as long as they are in contained use conditions, do these organisms become GMOs when they are not anymore under contained use.

The relevance of the Court ruling regarding the contained use of GMOs is unclear for some Member States (Bulgaria, Ireland), as the scope of the Directive covers only GMMs. Therefore, when national legislations were extended to cover GMOs, it is not clear (for Bulgaria and Italy[58]) if the contained use of GMO should follow Directive 2001/18/EC or Directive 2009/41/EC, in particular with respect to the definition of GMO and the exclusion criteria. The Commission clarifies that Directive 2001/18/EC covers the deliberate release of GMOs into the environment and their placing on the market. Deliberate release means any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment. Therefore, Directive 2001/18/EC does not cover the contained use of GMOs.

Italy and Bulgaria would consider useful to extend the scope of the Directive to all GMO and to establish unified requirements for contained use of GM plants and animals.

For Germany, the Directive seems not adequate for the risk assessment of genome-edited, self-cloned organisms resulting from SDN3 techniques and additional questions are raised whether the application of certain techniques (CRISPR-Cas9 variants like dCas9 with non-functional nuclease, or dCas13 variant only modifying RNA) lead to the creation of GMO. Finland would like clarifications specifically in the context of deletion mutagenesis where no foreign DNA is inserted in the genome, regarding the legal status of the progeny of GMOs that do not inherit the modification, and on the legal status when an existing mutant organism is reverted to wild type using novel mutagenesis techniques.

The Netherlands stated that the Court has not explained what constitutes mutagenesis, nor how to determine when mutagenesis techniques or methods have traditionally been used and have proven to be safe. This last point is also shared by Germany.

Bulgaria and Finland would welcome clarifications from the Commission Legal Service.

In this legally uncertain situation, Finland reported that the Board for Gene Technology has made a non-consensus interim decision that contained use is out of scope of the Court's ruling. The legal status of new mutagenesis techniques in contained use is currently evaluated by the Board on a case-by-case basis, as some variations of these techniques (e.g. gene drives) may result in GMOs.

For Bulgaria, the topic of new genomic techniques shows that it is increasingly difficult to accommodate the developments of modern biotechnology by non-legislative means, and the possibility to amend or fully update the European GMO legislation should be considered.

For the Netherlands, the Court's ruling urges the legislator to keep the Directive up-to-date in respect of technical and scientific progress, and it is urgent that the scope of what is to be

[58] Italy comment to the question "Has the scope of the transposing legislation been extended to the contained use of GM plants and GM animals in your Member State?": "*According to 2001/18/EC Directive, the contained use of GMOs (e.g. for testing/research purposes) should be carried out by implementing containment measures based on the same principles as laid down in 90/219/EEC: it is not expected any notification to CAs. Contained uses of GMOs are non-regulated activities, both at EC and national levels*."

understood by mutagenesis is clarified by authorities or the EU-legislator in order to provide clarity and legal certainty.

Finland and the United Kingdom suggests to review the definition of genetic modification in the Directive, and possibly to evaluate the pros and cons of technology-based regulation versus trait-based regulation when dealing with a rapidly developing technology.

Lithuania remarked that it would be helpful to have information on risk assessment methodology and safety measures to use for each new genomic technique, and would also welcome harmonised EU legislation of new mutagenesis techniques.

6.2 Other difficulties for interpretation of the Directive

Some other issues for interpretation of the Directive related to its definitions: for example, for the Czech Republic, whether a specific sub-cellular element falls under the definition of "micro-organism" or not. The Czech Republic considered that plasmids are not GMOs, and that a DNA vaccine does not fall under the scope of the Directive (although during the development phase, the vaccinated animals should be treated as GMOs until appropriate studies prove that the plasmid DNA has not been integrated into the host genome).

The concept of "premises" was also unclear in certain cases, and unanticipated needs for moving the GMOs temporarily to new premises for non-repeating procedures (such as photographing or scanning) may arise quickly in research laboratories, which can cause an administrative problem (Finland).

In Germany, some regional competent authorities encountered problems with the interpretation of Annex IV of the Directive and suggested a more precise wording of standards, while Slovakia would appreciate guidance regarding the isolation of the laboratory suite[59]. The Netherlands noted differences in interpretation of the Annexes between Member States.

Bulgaria, Spain and Hungary reported difficulties regarding clinical trials (see part III, p. 20).

6.3 Difficulties and solutions regarding the implementation of the Directive

Many Member States[60] have no further difficulties related to the implementation of the Directive. Aspects related to gene drive organisms are discussed in part IV of the report.

- Issues related to appropriate classification of the contained uses

Finland indicated that the classification of viruses and cell cultures has been problematic in some cases, in particular when pathogens have been attenuated, a problem faced also by Ireland. Sweden reported a problem to distinguish between class 1 and class 2 for GMM uses with a replication deficient virus vector, and Denmark mentioned that users are sometimes confused regarding the appropriate class for their laboratory work, in particular when working with adeno-associated virus vectors.

[59] "*the laboratory is separated from other areas in the same building*" (Annex IV, table I A, point 1).
[60] BE, BG, EE, EL, FR, HR, CY, LV, LT, LU, HU, MT, AT, PL, PT, RO.

Some Member States would consider useful that the Commission provides clarification on the classification of pathogenic organisms when their pathogenicity has been attenuated (Finland), establishes a list of known biological agents in accordance to the hazards and in accordance with the classes of contained uses (Croatia), and more generally a list of generally regarded as safe (GRAS) laboratory strains, laboratory animals and cultivars adopted at EU level, as those account for most of the activities done at universities and research institutions (Bulgaria).

For difficult issues and cases of unclear risk assessment, some competent authorities consulted specifically their advisory committee and/or other competent authorities under the Directive to know for example how attenuated viral vectors were classified in other Member States. Ireland considered as a result of those consultations that attenuated lentiviral vectors should be classified as class 2 GMMs.

- Difficulties with notifications

Regarding the assessment of notifications and the corresponding burden, the United Kingdom estimates that the time spent in reviewing lower-risk class 2 activities is disproportionate due to the amount of information required and the volume of class 2 notifications received (~90% of notifications are for class 2 uses), and Sweden thinks that the notification procedure for Class 1 and Class 2 is of limited value, and that the information required could be simplified. Two Member States (Denmark, Ireland) refer to issues for class 1 notifications, the procedure being time consuming, while those activities present no or negligible risk to the environment.

The Commission clarifies that the Directive does not require notification of subsequent activities for class 1 (Article 7 "Following the notification referred to in Article 6, subsequent class 1 contained use may proceed without further notification").

Germany and Slovakia reported difficulties for notification of class 3 contained uses (handling and inactivation of the organisms, several contained uses reported in one single notification). In case of premises that have been the subject of a previous notification to carry out a class 3 or 4 contained use, Slovakia considers that the timeframe of 45 days for the competent authority to communicate its decision is too short (Article 9.2(a)).

To help improving the situation, some Member States updated their procedures: in Ireland, users are not required anymore to submit annual reports for class 1 GMM contained use activities, and the United Kingdom streamlined its notification system to spend less time assessing class 2 activities. Regarding actions at national level, Denmark mentioned that class 1 notifications could be taken out of the Danish legislation.

Ireland and the United Kingdom proposed to align the notification requirements with Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work[61]: Ireland suggests the alignment for class 1 GMM contained use activities , as that Directive does not require the notification of activities involving risk group 1 biological agents; and the United Kingdom suggests the alignment for class 2 contained use

[61] Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC) (OJ L 262 , 17/10/2000, p.21).

activities, as that Directive requires only the first class 2 contained use at a given premises to be notified. Then, subsequent class 2 contained uses could be carried out, following approval by an internal safety committee, without the need to notify the national competent authority. Alternatively, the information requirements for class 2 notifications could be minimised. Sweden also suggested that less information could be provided for class 1 and class 2 contained uses. Sweden noticed that Directive 2000/54/EC is currently under revision, and wondered if, in case some safety measures in its Annexes V and VI would be changed, this would impact the containment measures in Annex IV of the Directive.

Finland suggested a simplification in the notification requirements of Article 6 when the notifier is often changing premises.

Slovenia suggests that inclusion of safe organisms in Part C of the Annex II of the Directive could contribute to reduce the size of the notifications, and the United Kingdom specifically refers to the inclusion, by the Commission, of a list of multiply disabled vectors for class 1 contained uses, which would provide greater delineation of class 1 and 2 contained uses and minimise the degree of over classification.

- Other issues

Two Member States (Finland and the Netherlands) noted issues related to disinfectants: the development of chemicals legislation has led to a situation where few effective disinfectants are available for pathogenic GMMs. Users in the laboratories are also poorly informed about the suitable disinfectants currently available for their particular GMMs, and sometimes use disinfectants that have not (yet) been admitted as a biocide for use under laboratory conditions.
Here the Commission notes that competent authorities should intervene when seeing that "*Users in the laboratories are also poorly informed about the suitable disinfectants currently available for their particular GMMs, and sometimes use disinfectants that have not (yet) been admitted as a biocide for use under laboratory conditions."*

Romania expressed a need and priority for further guidance on the risk assessment of living modified (LM) fish, LM organisms produced through synthetic biology, LM soil dwelling organisms, and LM birds.

Finally, the Netherlands encountered differences in the strict GMO-regulations and the less strict regulation of wild type pathogens, which could partly be explained by the implementation of the legislation in the Netherlands, but seemed also caused by a lack of harmonisation at EU level.

Some Member States managed to solve issues identified in the previous reporting period, for example, by asking advice to their scientific advisory bodies/experts. Other Member States (Bulgaria, Spain, Lithuania, Poland and Slovenia) reported communication activities to increase awareness and share best practices regarding contained uses activities among users, such as update of guidance documents, publication of brochures with examples of notification forms, and/or to engage with other experts to shared knowledge and experience.

Italy, the Netherlands and Finland consider that discussions and/or actions at EU level might be helpful, for example on disinfectants, and more generally, a better cooperation among the

national competent authorities and harmonised approaches at EU level (Italy), together with further training (Malta).

PART II: OVERVIEW OF CONTAINED USES AND PREMISES

Information on the number of notifications and amendments submitted for contained uses of GMMs, number of premises and number of contained uses of GMMs reported by each Member State, are provided in the accompanying Commission Staff Working document. For those Member States that have extended the scope of the Directive to the contained use of GM animals and GM plants[62], information on the number of notifications for contained uses of GMOs submitted is also provided in the Commission Staff Working document.

Table 1: Overview of authorised classes of contained uses in the Member States

Class of use	Number of MS	
No notifications	2	Greece, Malta
Class 1 only	2	Bulgaria, Latvia
Up to class 2	9	Denmark , Croatia, Cyprus, Lithuania, Luxembourg, Hungary, Romania, Slovenia, Finland
Up to class 3	11	Belgium, the Czech Republic, Estonia, Ireland, Spain, Italy, the Netherlands, Austria, Poland, Portugal, Slovakia
Up to class 4	4	Germany, France, Sweden, the United Kingdom

Of note, some Member States[63] do not make distinction between GMM, GM plants and GM animals in notification procedures, therefore the data reported is a total of contained uses of GMMs and GMOs.

The majority of the Member States[64] that received notifications for GM plants or GM animals did not encounter specific challenges related to those. Still, Poland reports challenges in the environmental risk assessment, while Sweden estimates there could be difficulties in the future for assessing the risks, as there is no classification system for contained uses of GMOs and the assessment is case-by-case.

PART III: INVESTIGATIONAL MEDICINAL PRODUCTS THAT CONTAIN OR CONSIST OF GMOs

1. Notifications and authorisations for manufacturing and/or administration

Eleven Member States authorise under the Directive the manufacturing and the administration of investigational medicinal products for human use that contain or consist of GMOs (Belgium, Greece[65], France, Italy, Luxembourg[66], Malta[67], Austria, Poland, Portugal, Finland and the United Kingdom). Among those countries, only Belgium, France, Italy, Portugal (for

[62] All, except EE, EL, IT, CY, LV, LU, RO.
[63] DE, NL, UK.
[64] BE, IE, CZ, DK, FR, HR, HU, NL, AT, PT, SI, SK, UK.
[65] Manufacturing was auhorised only in 2018, administration authorised only in 2014-2017.
[66] Manufacturing was authorised only in 2014-2017.
[67] Only in 2018.

manufacturing only), Finland and the United Kingdom had notifications and authorisations. The majority of those related to Advanced Therapy Medicinal Products ("ATMPs"), mostly under class 1 and 2 of contained use (when specific information was known by the competent authority).

Most of these Member States[68] (except Malta and Poland, and with the addition of Slovenia[69]) also authorise manufacturing and administration of investigational medicinal products for veterinary use, with very few notifications submitted and authorisations given.

Some other Member States authorise only the manufacturing but not the administration of investigational medicinal products under the Directive: Bulgaria, the Czech Republic, Germany, Spain, Hungary and Romania for human and veterinary uses, and Ireland for human use only. One Member State (Denmark) authorises only the administration, and not the manufacturing of those products (for both human and veterinary uses).
Finally, eight Member States do not authorise the use of the products under the Directive, nor for manufacturing, nor for administration (Estonia, Croatia, Cyprus, Latvia, Lithuania, the Netherlands, Slovakia and Sweden).

Table 2: authorisation of investigational medicinal products under the Directive, and total number of authorisations

	Human use		**Veterinary use**	
	Manufacturing	**Administration**	**Manufacturing**	**Administration**
BE	Yes / 10	Yes / 66	Yes / 0**	Yes / 2
BG	Yes / 0	No	Yes* /0	No
CZ	Yes / 0	No	Yes / 0	No
DE	Yes / N.D	No	Yes / N.D	No
DK	No	Yes / 12	No	Yes* / 0
EE	No	No	No	No
IE	Yes* / 0	No	No	No
EL	Yes* / 0	Yes* / 0	Yes / 0	Yes* / 0
ES	Yes */ N.D	No	Yes * / N.D	No
FR	Yes / 5	Yes / N.D	Yes / N.D	Yes* / N.D
HR	No	No	No	No
IT	Yes / 11	Yes / 51	Yes / 0	Yes / 0
CY	No	No	No	No
LV	No	No	No	No
LT	No	No	No	No
LU	Yes* / 0	Yes / 0	Yes / 0	Yes / 0
HU	Yes* / 0	No	Yes* / 10	No
MT	Yes* / 0	Yes* / 0	No	No
NL	No	No	No	No
AT	Yes / 0	Yes / 0**	Yes / N.D	Yes / N.D
PL	Yes / 0	Yes / 0	No	No
PT	Yes / 3	Yes / 0	Yes / 0	Yes / 0

[68] For Greece and France: administration was authorised only in 2014-2017.
[69] Manufacturing and administration only in 2018.

RO	Yes* / 0	No	Yes* / 0	No
SI	No	No	Yes* / 0	Yes* / 0
SK	No	No	No	No
FI	Yes / 7	Yes / 13	Yes / 0	Yes / 0
SE	No	No	No	No
UK	Yes / N.D	Yes / N.D	Yes / N.D	Yes / 1

* indicates that only in one period (either 2014-2017, or 2018), the Member State' reply was "yes".
** some notifications were submitted but 0 authorisation.
N.D: not determined

2. Challenges regarding the manufacturing activities

The majority of Member States report no specific challenges (or no relevance as this activity is not taking place) in implementing the Directive for the manufacturing of investigational medicinal products that contain or consist of GMOs for human or veterinary uses.

Belgium noticed that in some cases the manufacturing of investigational medicinal products has been made in another country and wonder to what extent all the data need to be checked.

Several Member States (Belgium, Germany, Italy and Finland) mentioned that different (control) authorities can be involved in data package evaluation, authorisation, and control of the activity/premises, and this can be challenging. It is suggested (Finland) that the interplay of contained use, good manufacturing practice (GMP), occupational safety (protection of workers from exposure to biological agents), and the Access and Benefit Sharing Regulation[70] is clarified, to avoid unnecessary regulatory burden for the operators and authorities involved.

Regarding veterinary use, in case of challenges, they are not different compared to the ones reported for human use, just Finland notes that it is more difficult to find national experts on the risk assessment for veterinary use. Finland suggests forming a network of experts that competent authorities could refer to when needed.

Some Member States (Belgium, Italy and Poland) proposed increased cooperation and information sharing among Member States, and among experts involved in the evaluation of different aspects of the medicinal products (safety, biosafety, quality).

3. Challenges regarding the administration activities

Regarding the administration of investigational medicinal products for human use that contain or consist of GMOs, Finland and Italy report that the submission of notifications in case of multicentre clinical trials is challenging. The concept of "notifier" (company developing the product, the CRO (contract research organisation), the hospital, etc.) is not always clear, and further sharing of information between the different actors involved is needed so that the notification is complete. In addition, Finland notes that challenges can arise from the interplay of various regulations concerning GMOs, pharmaceuticals, occupational safety, waste treatment, and patient rights.

[70] Regulation (EU) No 511/2014 of the European Parliament and of the Council on compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization in the Union

Belgium, Bulgaria, Spain, France, Italy, Hungary, Portugal, Romania, Finland and Sweden[71] underline the difficult distinction between contained use or deliberate release for clinical trials with GMOs, and the fact that Member States have different interpretations and approaches. This creates difficulties for the competent authorities, and also for companies and users, in particular in case of clinical trials in different countries (with then different requirements).

For example, for Spain, it is not clear whether facilities in which GMOs are handled or stored must be notified for contained used activities. In Sweden, only preparations and sample analysis may be notified as contained use, and this can create confusion for the users (which part of an activity is contained use, and which part is not). For Bulgaria, it is not clear how the provisions of the Directive should be applied when GMM is administered in hospital during clinical trial but the patients are not kept under contained conditions for the duration of the trial.

For Italy, it is also a challenge to establish the relevant cases for which a risk assessment has to be submitted by a notification or not, if a medicine used in the clinical trial has obtained the marketing authorisation by EMA centralized procedure. In these cases, the risks to consider could be different for a new clinical trial if compared to those assessed in order to obtain the marketing authorisation. This last aspect need to be assessed on a case by case basis by the Italian competent authority.

The Commission specifies that clarification about the authorisation under the GMO framework in case of clinical trials with investigational products that have a marketing authorisation has been given in the document "Medicinal products for human use containing or consisting of GMOs: interplay between the EU legislation on medicinal products and GMOs – Frequently asked questions"[72].

Regarding the administration of investigational medicinal products for veterinary use that contain or consist of GMOs, further specific comments relate to the difficulty to assess if notifications are for clinical trials or for research and development (Belgium), to the fact that risk management methods are challenging if the test subjects are pets or companion animals (Finland). Sweden reports that a future challenge may be a clinical trial with caged animals.

Some solutions have been implemented at national level. In Sweden, respective competent authorities collaborate to help the users. When the framework to be followed is not clear, Belgium recommends applicants to request advice from the Federal Agency for Medicines and Health Products prior to the submission of the clinical trial application. In addition, the competent authority, in collaboration with the Belgian federal agency for medicines, is preparing a document "guideline" aiming to help applicants in determining the regulatory procedures they must follow. Germany reported that an administrative agreement was reached in March 2015 between the relevant federal and competent authorities regarding the distinction between genetic engineering activities in containment and approval of clinical trials with GMOs. In the United Kingdom, the competent authority is discussing with the

[71] Spain and Sweden regulates clinical trials with GMOs as deliberate release activities. In Belgium, depending on the characteristics and mode of administration of the medicinal product, it is possible that clinical trials with GMOs medicinal products for human use do not require an authorisation under the deliberate release Directive. Bulgaria and Portugal define the legal framework of the GMOs clinical trial on a case-by-case basis, taking into account the specificity of the GMO clinical trial.

[72] Available at: https://ec.europa.eu/health/human-use/advanced-therapies_en

medicines regulator to see if there are ways to streamline clinical trials whilst complying with requirements under the different regimes.

However, various Member States stressed that addressing issues related to the legal framework for clinical trials with GMMs should be done at EU level. France and Portugal would welcome clarifications on the legislative framework to be applied. Spain would like to have harmonised guidelines at EU level in order to clarify whether clinical trials have to be carried out under the scope of the Directive or/and of the Directive 2001/18 /EC. Bulgaria, Spain, Italy and Portugal consider that there should be a harmonisation of the procedures for the notification and evaluation of clinical trials with GMMs at EU level (and also of guidance, for Portugal). In addition, the notification process should be improved and simplified for Italy, which suggests amending the Directive and Directive 2001/18/EC with ad hoc provisions focused on clinical trials in which investigational medicinal products (IMPs) are administered. Finally, for Italy, a harmonised approach at EU level would allow the Commission and Member States to be informed about clinical trials authorised under the Directive and to publish the relevant information on the Commission website.

Bulgaria, Italy, Finland and the United Kingdom expect that the Ad-hoc working group on the interplay between the GMO legislation and the legislation on medicinal products will clarify the situation of clinical trials with GMMs, through provision of better information and guidance on risk assessment of certain types of vectors etc.

The Ad-hoc working group on the interplay between the GMO legislation and the legislation on medicinal products was set up as a result of demands from Member States' competent authorities and stakeholders to address a number of issues relating to the interplay between the GMO legislation and the legislation on medicinal products, with the objective to seek practical ways to address the identified issues within the existing regulatory framework.

Finland also suggests examining whether GMO medicinal product production and clinical trials should be legally separated from GMO directives.

PART IV: GENE DRIVE MODIFIED ORGANISMS

1. Notifications and measures taken regarding gene drive modified organisms

Three Member States (Germany, France[73] and Italy) reported notifications for gene drive modified organisms (GDOs)[74] submitted under their contained use legislation: on Drosophila melanogaster for basic research (class 1 – Germany), on Anopheles gambia and Anopheles arabiensis for the development of GM mosquitoes for malaria control (class 2 – Italy).

In addition, some Member States (Germany, France[75], the Netherlands, Sweden and the United Kingdom) took measures regarding GDOs under the Directive, involving their advisory board for scientific guidance, or by amending their procedures.

[73] France did not report additional information about the received notifications.
[74] For the purpose of this report, the definition of "gene drive" is a system of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced.
[75] France did not report additional information about the measures taken.

More notably, Germany involved its advisory board, which issued a position statement according to which activities generating GDOs are classified as class 2. The recommendation of specific safety measures will be done by the advisory board on a case by case assessment. Germany also provided details about the specific containment measures implemented for the contained use of gene drive modified Drosophila to prevent their escape.

The Netherlands amended their GMO contained use legislation: it requires for all applications for GDOs a permit instead of a notification. Their national legislation allows for imposing specific containment measures on top of, or as an alternative for, the general containment measures.

Sweden differentiates the contained use of GDOs according to the type of the organism. If a GMM would be modified with a gene drive mechanism, it should be at least considered as class 2, with a specific risk assessment (focus on the risks in case of unintended release of the GMM). For GM animals, the notification form will be amended if there will be future notifications concerning gene drive animals.

The competent authority of the United Kingdom issued guidance on gene editing and gene drive (prepared by its scientific advisory committee) to advise users of configurations of CRISPR Cas9 that would raise concerns.

2. Possible challenges regarding the contained use of gene drive modified organisms

Various Member States reported that their experience with contained use of GDOs is relatively limited and some anticipate possible challenges.

First, regarding the scope of the Directive, Bulgaria, Finland, Italy, Sweden and the United Kingdom noted that the vast majority of potential GDOs are likely to be animals (insects and rodents) and plants. Therefore, they would be outside of the scope of the Directive, which covers only GMMs, and would not require a notification[76]. Sweden is of the opinion that the issue may be more relevant for the Directive 2001/18/EC (since gene drive concerns eukaryotic organisms).

The United Kingdom explained that it is difficult to regulate GDOs under the Directive, even if GM plants and animals are included in its national legislation (as in many other Member States) because there are no activity notification requirements (or class of work) for GM plants/ animals. For Finland, additional legal measures may be necessary for Member States that only regulate GMMs in their national contained use legislation, while for Bulgaria, harmonisation of requirements for contained use of GDOs, other than gene drive modified micro-organisms, between Member States is an open issue.

Regarding the risk assessment and risk management of those organisms, Belgium, Bulgaria, Ireland, Italy, Lithuania, the Netherlands, Romania, Finland and Sweden anticipate possible challenges, in particular for environmental risk assessment, correct classification and appropriate containment measures.

[76] The Commission notes that if a Member State' national legislation has been extended to GM animals and plants, a notification will be required.

Italy reported difficulties as no specific provisions are laid down in the Directive for the contained use of GDOs. The Netherlands also underlined that the classification system of the Directive and the corresponding containment measures focus on the pathogenicity of the GMM, while the biology of GDOs may require different containment measures. Belgium noted in particular the specific characteristics of the GDOs to be considered, such as the rapid spread of the carried modification through several generations of target or non-target organisms and the potential risks for the environment (while in general the GDO will not be pathogenic).

Some Member States stressed the importance of a case-by-case approach, even more as different groups of GDOs have different reproductive and ecological characteristics (Belgium, Bulgaria, Italy).

Finland also noticed that if the user has already an existing notification for class 1 use, it could start a new class 1 activity without a new notification, and if the user has classified the GDO in the risk assessment into class 1, the competent authority would not be informed about such activity with GDO before an inspection of the premises.

Belgium, Italy, the Netherlands and Sweden noted that some adaptations should be considered for GDOs (additional requirements, higher containment level and control measures) to ensure that performed activities with those organisms can be considered safe for the humans, animals and environment. Still, for Belgium, and Sweden, a proper risk assessment (case-by-case procedure) will catch possible risk with such GMMs and the Directive remains appropriate for the protection of the environment and workers for contained use of gene drive modified micro-organisms.

Bulgaria mentioned that it may be appropriate to consider initially that any GDO will pose high risk for the environment and to apply stringent containment measures. Such measures should use at least two different containment strategies suitable for the specific modified organism.

The United Kingdom highlighted that there is a lack of consistency in the approach across Member States with regard to activities with GDOs.

More broadly, several Member States (Spain, France, Italy, Lithuania, Hungary, the Netherlands, Poland and Finland) suggested to have discussion and exchange of information at EU level, on experience and activities with GDOs under contained use. They would welcome harmonised guidelines at EU level regarding procedure for GDOs including notification, risk assessment methodology, containment measures and control requirements. This could possibly result in an amendment of the Directive (Italy, the Netherlands).

Finally, Bulgaria and the Netherlands mention that GDOs could move across borders, and therefore it is important for those countries to establish mechanisms for fast and effective cooperation between Member States if such organisms are released into the environment, deliberately[77] or accidentally. The Netherlands would welcome an EU guidance on how to inform Member States in case of a high-risk incident with GMM or GMO, which should be explicitly extended to GDOs.

[77] The Commission notes that the Directive 2001/18/EC applies in case of deliberate release in the environment of GMOs.

SUMMARY AND CONCLUSIONS

Member States reported their experience with the Directive for the period 2014-2018 to the Commission. This report summarises those contributions (available in the Annex) and covers notification and approval systems, risk assessment and classification of contained uses, accidents, inspection and enforcement issues, and implementation of the Court ruling on new mutagenesis techniques, for the contained use of GMMs.

Some clarifications from the Commission are also added in this report, to address Member States' comments.

It should be noted that the vast majority of Member States has extended the scope of their transposing legislation to the contained use of GM plants and GM animals, and in some countries, the transposing legislation is stricter than the Directive (notifications for Class 1 contained uses, waste inactivation for all classes).

Few Member States reported changes regarding the notification and approval systems as compared to the period 2009-2014. During period 2014-2018, most Member States processed the notifications within the statutory timeframe. When delays occurred, they concerned usually less than 15% of the assessed notifications and Member States took actions to reduce and prevent such delays. However, many noted the increasing complexity of the notifications, which makes the processing time longer. Member States reported difficulties related to the quality and completeness of the submitted notifications, and difficulties linked to the definitions of the Directive and the correct classification of the contained uses. They also stressed the administrative burden of the notification system. Some Member States suggested changes in the Directive, for example to review the definition of genetic modification in the Directive, or amending the notification requirements for class 1 and 2 of contained uses.

Regarding waste, in some Member States the waste from contained use activities is recycled after inactivation. Inspection procedures put in place by the Member States included regular inspections to evaluate in particular the compliance with the Directive, the correctness of the risk assessment classification, the effectiveness of the respective containment level. The number of inspections carried out during the reporting period varies among Member States, from 10 to 100% of the premises controlled. Very few Member States reported accidents, or some incidents. In general, when public consultations are carried out, no comments are submitted. In several Member States, information on the premises for contained use of GMMs and GMOs is maintained updated and available online.

The national reports show an emphasis on increased communication between users and competent authorities, to increase awareness and share best practices regarding contained uses activities among users.

While many Member States reported no specific difficulties regarding the interpretation of the Directive, those that reported issues often refer to problems with the definition of GMMs/GMOs in the context of new genomic techniques, and synthetic biology.
Member States are receiving notifications for contained use of GMMs/GMOs obtained with new mutagenesis techniques. Regarding the impact of the Court ruling on new mutagenesis, a number of countries indicated that it has no impact as risk assessment and management of

contained uses of GMMs and GMOs obtained by new techniques are performed in the same way as other GMOs. On the other hand, some Member States mentioned difficulties in applying and enforcing the contained use legislation for GMOs obtained through new genomic techniques due to their detection and identification, and the difficulty to distinguish them from organisms obtained by classical mutagenesis or naturally. A few Member States pointed out some legal uncertainties about the application of the Directive in the light of the Court ruling.

There are also differences among Member States regarding the manufacturing and administration of investigational medicinal products for human or veterinary use that contain or consist of GMOs. Some Member States authorise one or both activities (manufacturing/administration) under the Directive while others do not. The difficult distinction between contained use or deliberate release for clinical trials with GMOs, and the fact that Member States have different interpretations and approaches, create difficulties for the competent authorities, and also for companies and users.

Various Member States stressed that addressing issues related to the legal framework for clinical trials with GMMs should be done at EU level and some expect that the Ad-hoc working group on the interplay between the GMO legislation and the legislation on medicinal products will clarify the situation of clinical trials with GMMs, through provision of better information and guidance on risk assessment of certain types of vectors etc.

Regarding gene drive modified organisms, only few Member States reported notifications submitted under their contained use legislation, for basic research or for the development of GM mosquitoes for malaria control. Some Member States took measures regarding GDOs under the Directive, involving their advisory board for scientific guidance, or by amending their procedures. Various Member Sates anticipated possible challenges, in particular for environmental risk assessment, correct classification and appropriate containment measures of GDOs. Some also pointed out difficulties to regulate GDOs under the Directive, even in cases where the national transposing legislation has been extended to cover GM plants and animals.

For some Member States, additional legal measures and/or harmonisation may be necessary between Member States, in particular for the ones that only regulate GMMs in their national contained use legislation. Several Member States consider that it might be helpful to exchange information on experience and activities with GDOs under contained use. They would welcome harmonised guidelines at EU level regarding procedure for GDOs including notification, risk assessment methodology, containment measures and control requirements.

More broadly, there is a need for better cooperation among the national competent authorities and harmonised approaches at EU level in relation with the interpretation and implementation of the Directive.