

**THE REGULATION OF SYNTHETIC BIOLOGY**  
**A GUIDE TO UNITED STATES AND EUROPEAN UNION REGULATIONS, RULES AND GUIDELINES**  
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**INTRODUCTION**

The field of synthetic biology encompasses the design and construction of new biological parts, devices, and systems, as well as the re-design of existing, natural biological systems for useful purposes. Although synthetic biology is a relatively new field, regulations applied to more traditional biological research already apply to synthetic biology and its products. This regulatory landscape was brought about by the advent of recombinant DNA technology, which has been used in research for decades. Most, but not all, synthetic biology research involves the use of recombinant DNA or synthetic DNA that is identical to DNA from existing organisms. This review treats US and EU regulations governing synthetic biology, the real world implementation of these regulations, and several treaties and agreements to which the US and EU are parties. The concluding section compares US and EU regulations and discusses future considerations for the regulation of synthetic biology.

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## **UNITED STATES FEDERAL REGULATIONS AND GUIDELINES**

This section summarizes US Federal regulations and guidelines that affect those working in the area of synthetic biology and discuss their applicability and penalties. Although these regulations exist on paper, not all are enforced and some are not enforceable. Furthermore, NIH guidelines, which are the most comprehensive guidelines for work in synthetic biology, are not binding on all individuals working in synthetic biology. Accordingly, after each summary, we discuss levels of enforcement and repercussions associated with non-compliance.

### **I. National Institutes of Health - Guidelines for Research Involving Recombinant DNA Molecules<sup>2</sup>**

While they are not always invested with binding regulatory authority, the National Institute of Health Guidelines for Research Involving Recombinant and Synthetic Nucleic Molecules (NIH Guidelines), are perhaps the most relevant feature of the regulatory landscape, as they are the regulations with which the vast majority of researchers are most familiar. The NIH Guidelines for working with recombinant DNA<sup>3</sup> are intended to specify safety practices and containment procedures including the creation and use of organisms and viruses containing recombinant DNA defined as “(i) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above”<sup>4</sup> Institutions involved in conducting or sponsoring any recombinant DNA research funded in part, or whole, by the NIH are required to adhere to the guidelines. In addition, funding from other federal agencies or private sources may often be contingent on compliance with the guidelines. Indeed, the NIH Guidelines are widely regarded as *de facto* standards within the research community and are often implemented by researchers who would otherwise not be obligated to do so.

Under NIH guidelines, experiments involving recombinant DNA are classified into six categories, based upon the number of regulatory hurdles they are required to clear to receive approval. The most dangerous experiments require IBC (Institutional Biosafety Committee) approval, RAC (Recombinant DNA Advisory Committee) review *and* NIH director approval prior to initiation of a proposed experiment while non-exempt experiments considered the least dangerous only require IBC notice which can be given on initiation of the proposed experiment. See Table 1 for more detailed information on experiments that fall into each of the six categories listed below.

- Experiments that require IBC approval, RAC Review, and NIH Director approval *prior to* initiation of the proposed experiment
- Experiments that require NIH/OBA and IBC approval *prior to* initiation of the proposed experiment
- Experiments that require IBC and IRB approval and RAC review *prior to* research participant enrollment
- Experiments that require IBC approval *prior to* initiation of the proposed experiment
- Experiments that require IBC notice *simultaneous* with initiation of the proposed experiment
- Exempt experiments

**IBC Approval:** All non-exempt experiments involving recombinant DNA require Institutional Biosafety Committee (IBC) review where they are evaluated to ensure the containment levels, facilities, procedures, practices, and training and expertise of personnel involved in the research are in compliance with the NIH guidelines. When no senior regulatory committee is involved, the IBC is also responsible for setting containment levels (as specified by the NIH) when whole plants or animals are used, reviewing recombinant DNA research to insure compliance with the NIH Guidelines, and adopting emergency plans covering accidental releases and personnel contamination resulting from recombinant DNA research. It is the responsibility of the IBC to report any significant problems with, or violations of the NIH Guidelines to the appropriate institutional official.

**RAC Review:** The Recombinant DNA Advisory Committee (RAC) functions to provide recommendations and advice to the Director of the NIH on the conduct and oversight of potentially dangerous research involving recombinant DNA. Experiments requiring RAC review must be performed using the containment levels assigned by the committee. Furthermore RAC has the authority to approve or deny experiments considered as Major Actions (see Table 1) under the NIH Guidelines.

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<sup>2</sup> Information in this section was taken from “NIH Guidelines for Research Involving Recombinant DNA Molecules” April 2002 and the May 2011 revisions unless otherwise noted. See [http://oba.od.nih.gov/oba/rac/Guidelines/NIH\\_Guidelines.htm](http://oba.od.nih.gov/oba/rac/Guidelines/NIH_Guidelines.htm) accessed November 1, 2011.

<sup>3</sup> Defined as either “molecules that are constructed outside living cells by joining natural or synthetic DNA molecules that can replicate in a living cell, or...molecules that result from the replication of those described above.” “NIH Guidelines for Research Involving Recombinant DNA Molecules”, April 2002, Section I-B. “Definition of Recombinant DNA Molecules”.

<sup>4</sup> NIH Guidelines for research involving recombinant DNA molecules (NIH Guidelines). April 2002. [http://www4.od.nih.gov/oba/rac/guidelines\\_02/NIH\\_Guidelines\\_Apr\\_02.htm#\\_Toc7261549](http://www4.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm#_Toc7261549).

Table 1. Required Actions Under NIH Guidelines by Experiment Type		
Experiment Type	NIH Guideline Section	Required Actions
Experiments involving the deliberate transfer of a drug resistance trait (that could compromise the use of the drug to control disease agents in humans, animals, or plants) to microorganisms that are not known to acquire the trait naturally	Section III-A-1-a - "Major Actions"	IBC approval, RAC Review, and NIH Director approval <i>prior to</i> initiation of the proposed experiment
Experiments involving the cloning of toxin molecules with LD50 < 100 nanograms/kilogram body weight	Section III-B-1	NIH/OBA and IBC approval <i>prior to</i> initiation of the proposed experiment
Experiments involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA into one or more human research participants	Section III-C-1	IBC and IRB approval and RAC review <i>prior to</i> research participant enrollment
Experiments using Risk group <sup>5</sup> 2, 3, 4 or restricted (select) agents as host-vector systems	Section III-D-1	IBC approval <i>prior to</i> initiation of the proposed experiment
Experiments in which DNA from Risk Group 2, 3, 4, or restricted (select) agents is cloned into nonpathogenic microbes	Section III D-2	IBC approval <i>prior to</i> initiation of the proposed experiment
Experiments involving the use of infectious DNA or RNA viruses or defective DNA or RNA viruses in the presence of helper virus in tissue culture systems	Section III-D-3	IBC approval <i>prior to</i> initiation of the proposed experiment
Experiments involving whole animals	Section III-D-4	IBC approval <i>prior to</i> initiation of the proposed experiment
Experiments involving whole plants to propagate such plants, or to use plants together with microbes or insects containing DNA or for other experimental purposes (e.g., response to stress).	Section III-D-5	IBC approval <i>prior to</i> initiation of the proposed experiment
Experiments involving more than 10 liters of culture	Section III-D-6	IBC approval <i>prior to</i> initiation of the proposed experiment
Experiments involving the formation of recombinant DNA molecules containing no more than two-thirds of the genome of any eukaryotic virus	Section III-E-1	IBC notice <i>simultaneous</i> with initiation of the proposed experiment
Experiments involving whole plants not previously covered in Section III-D-5	Section III-E-2	IBC notice <i>simultaneous</i> with initiation of the proposed experiment
Experiments involving transgenic rodents	Section III-E-3	IBC notice <i>simultaneous</i> with initiation of the proposed experiment
Exempt experiments	Section III-F-1, Section III-F-2, Section III-F-3, Section III-F-4, Section III-F-5, Section III-F-6	N/A

Table 2. NIH Risk Groups		
Risk Group	Description	Examples
RG1	Agents not associated with disease in healthy adult humans	asporogenic <i>Bacillus subtilis</i> or <i>Bacillus licheniformis</i>
RG2	Agents associated with human disease which is rarely serious and for which preventive or therapeutic interventions are <i>often</i> available	<i>Listeria</i> , <i>Staphylococcus aureus</i> , <i>Microsporium</i> , <i>Entamoeba histolytica</i> , Mumps virus
RG3	Agents associated with serious or lethal human disease for which preventive or therapeutic interventions <i>may be</i> available	<i>Yersinia pestis</i> , <i>Histoplasma capsulatum</i> , Yellow fever virus, TME agents
RG4	Agents likely to cause serious or lethal human disease for which preventive or therapeutic interventions are <i>not usually</i> available	Ebola virus, Lassa virus, Equine morbillivirus

<sup>5</sup> An explanation of the NIH Risk Groups is provided below.

The NIH has set up risk groups for microbial agents used in recombinant DNA research. These risk groups classify agents according to their relative pathogenicity for healthy human adults. An explanation of each risk group is given in Table 2. Using the risk group classifications the NIH has put forth guidelines specifying appropriate safety precautions that must be taken when using recombinant DNA with each group of agents. These guidelines are discussed briefly below.<sup>6</sup>

The guidelines regarding the NIH Risk Groups require that experiments involving the introduction of recombinant DNA into organism belonging to Risk Group 2, Risk Group 3, or Risk Group 4 (including defective viruses in the presence of a helper virus) be conducted at biosafety level 2, level 3, and level 4 respectively. Experiments involving the transfer of DNA from Risk Group 2 or 3 agents into a non-pathogenic (Risk Group 1) organism may be performed under BL2 containment. Importantly, the NIH guidelines state that, when transferring DNA from Risk Group 4 agents into nonpathogenic organisms, experiments should be performed under BSL4 containment until demonstration that “only a totally and irreversibly defective fraction of the agent’s genome is present in a given recombinant” at which time containment can be downgraded to BL2. Furthermore, the NIH recommends that experiments that are likely to enhance pathogenicity or extend the host range of viral vectors under conditions that permit a productive infection should be evaluated further and consideration given to increasing the BSL level by at least one.

Although the NIH risk groups encompass only microbial agents, guidelines also exist for experiments involving whole plants and animals. When experiments involve whole animals in which the animal’s genome has been altered or which involve viable microbes containing recombinant DNA (other than viruses that are only vertically transmitted) that are tested on whole animals, a minimum containment of BL2 or BL2-N<sup>7</sup> is required. However, cases where the introduction of recombinant DNA into animals might lead to the creation of novel mechanisms or increased transmission of a recombinant pathogen or production of undesirable traits in a host animal containment conditions should be tightened. When experimenting with animals that contain sequences from viral vectors that do not lead to transmissible infection as a result of complementation or recombination in the host animal, BL1 or BL1-N containment may be used.

The NIH recommends BL3-P or BL2-P+<sup>8</sup> biological containment for many experiments involving recombinant DNA and whole plants. Experiments under this containment level include: those involving “most exotic infectious agents with recognized potential for serious detrimental impact on managed or natural ecosystems when recombinant DNA techniques are used, infectious agents with recognized potential for serious detrimental effects on managed or natural ecosystems” in which there exists “the possibility of reconstituting the complete and functional genome of the infectious agent by genomic complementation *in planta*” and, experiments with “microbial pathogens of insects or small animals associated with plants if the recombinant DNA-modified organism has a recognized potential for serious detrimental impact on managed or natural ecosystems.”<sup>9</sup> BL3-P containment is recommended for experiments involving sequences encoding “potent vertebrate toxins introduced into plants or associated organisms” while BL4-P containment should be used when working with readily transmissible exotic infectious agents that have “the potential of being serious pathogens of major U.S. crops” when in the presence of their specific vectors.<sup>10</sup>

Notably, under the NIH Guidelines, synthetic DNA segments which are likely to be expressed to yield a potentially harmful polynucleotide or polypeptide (e.g., a toxin or a pharmacologically active agent) are considered as equivalent to their natural DNA counterpart. However, if the synthetic DNA segment is not expressed *in vivo* as a biologically active polynucleotide or polypeptide product, it is exempt from the NIH Guidelines. Other NIH exempt experiments include: “Those that consist entirely of DNA segments from a single non-chromosomal or viral

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<sup>6</sup> A full list of NIH guidelines as well as exemptions can be found at:

[http://www4.od.nih.gov/oba/RAC/guidelines\\_02/NIH\\_Guidelines\\_Apr\\_02.htm](http://www4.od.nih.gov/oba/RAC/guidelines_02/NIH_Guidelines_Apr_02.htm).

<sup>7</sup> BL2 and BL2-N refer to biosafety level two and biosafety level two-animals respectively. Standard practices for BL2 can be found at:

[http://www4.od.nih.gov/oba/RAC/guidelines\\_02/Appendix\\_G.htm](http://www4.od.nih.gov/oba/RAC/guidelines_02/Appendix_G.htm) and standard practices for BL2-N can be found at

[http://www4.od.nih.gov/oba/RAC/guidelines\\_02/Appendix\\_Q.htm#\\_Toc7256324](http://www4.od.nih.gov/oba/RAC/guidelines_02/Appendix_Q.htm#_Toc7256324).

<sup>8</sup> BL2-P and BL3-P refer to biosafety level two-plants and biosafety level three-plants respectively. Standard practices for BL2-P can be found

at: [http://www4.od.nih.gov/oba/RAC/guidelines\\_02/Appendix\\_P.htm#\\_Toc7255954](http://www4.od.nih.gov/oba/RAC/guidelines_02/Appendix_P.htm#_Toc7255954) and standard practices for BL3-P can be found at:

[http://www4.od.nih.gov/oba/RAC/guidelines\\_02/Appendix\\_P.htm#\\_Toc7255970](http://www4.od.nih.gov/oba/RAC/guidelines_02/Appendix_P.htm#_Toc7255970).

<sup>9</sup> Section III-D-5-e of the April 2002 revisions of the *NIH Guidelines for Research Involving Recombinant DNA Molecules*.

[http://www4.od.nih.gov/oba/RAC/guidelines\\_02/NIH\\_Guidelines\\_Apr\\_02.htm](http://www4.od.nih.gov/oba/RAC/guidelines_02/NIH_Guidelines_Apr_02.htm)

<sup>10</sup> Section III-D-5-c of the April 2002 revisions of the *NIH Guidelines for Research Involving Recombinant DNA Molecules*.

[http://www4.od.nih.gov/oba/RAC/guidelines\\_02/NIH\\_Guidelines\\_Apr\\_02.htm](http://www4.od.nih.gov/oba/RAC/guidelines_02/NIH_Guidelines_Apr_02.htm)

DNA source, though one or more of the segments may be a synthetic equivalent”; “those that consist entirely of DNA from a prokaryotic host including its indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species), or when transferred to another host by well established physiological means”; “Those that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, through one or more of the segments may be a synthetic equivalent.”; “Those that do not present a significant risk to health or the environment, as determined by the NIH Director, with the advice of the RAC, and following appropriate notice and opportunity for public comment.”<sup>11</sup> Under the guidelines, exact copies of dangerous genes are not covered if not made by recombinant methods. This gap is addressed through proposals for reform treated at the end of this section.

In March 2009 and April 2010, NIH published proposals to update the NIH Guidelines to cover explicitly research using synthetic DNA. These actions were a result of the NSABB recommendation that the US Government examine the language and implementation of current biosafety guidelines to ensure that they cover research with chemically synthesized DNA. The proposed amendments would broaden the scope of the Guidelines, which currently cover DNA molecules that are created via recombinant techniques, to encompass nucleic acids that are synthesized without the use of recombinant techniques. The name of the Guidelines would also be changed to “NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules.”<sup>12</sup> The revised proposal published in April 2010 would substantially modify Section III-E-1. The proposal would “allow containment to be lowered provided the ability of the virus to replicate has been irreversibly impaired by a complete deletion in one or more capsid, envelope or polymerase genes required for viral replication. A quantitative criterion based on the amount of the genome present would also be maintained.” The proposed revision recognizes the importance of intrinsic strategies of containment and creates incentives for the redesign of organisms to limit replication.<sup>13</sup>

**Applicability and Enforcement of NIH Guidelines:** While difficult to enforce, many of the NIH guidelines regarding the use of recombinant DNA molecules are typically followed by investigators. Although some grey areas surrounding the guidelines exist, the NIH director may aid in the interpretation of NIH guidelines for experiments not specifically addressed by the guidelines. Note that although most experiments involving synthetic biology involve the manipulation of DNA and therefore may be subject to NIH regulation, many experiments involving synthetic biology would be classified as exempt. Noncompliance with NIH guidelines may result in penalties for both the violator and the institution that supports the violator even if the violator is not a recipient of NIH funding. Penalties may include suspension, limitation, or termination of financial assistance for the violators NIH-funded research projects and similar penalties for other NIH funded recombinant DNA research at the same institution. Alternatively researchers at the violator’s institution may be required to obtain prior NIH approval of any or all recombinant DNA projects at the institution. As mentioned above, these guidelines are not enforceable for researchers that are not affiliated with an institution that receives NIH funding. Furthermore, because much of the local enforcement of these guidelines is left to individual institutional biosafety committees, the stringency of enforcement varies in practice from institution to institution.

## **II. Environmental Protection Agency, US Department of Agriculture and Food and Drug Administration**

NIH guidelines address research involving recombinant DNA. By contrast, EPA, USDA and FDA regulate the use and commercial production of genetically modified microbes, plants, and food and drugs. Unlike the NIH guidelines, the EPA, USDA and FDA regulations apply primarily to the products of synthetic biology research that will be used for commercial purposes.

### **A. Environmental Protection Agency**<sup>14</sup>

The EPA regulates the development and production of “new”<sup>15</sup> microbes “for commercial purposes” created via recombinant genetics under authority from the Toxic Substances Control Act (TSCA) (15 U.S.C. 2615).<sup>16</sup> Anyone

<sup>11</sup> A list of natural exchangers that are exempt from the NIH guidelines can be found at: [http://www4.od.nih.gov/oba/RAC/guidelines\\_02/APPENDIX\\_A.htm](http://www4.od.nih.gov/oba/RAC/guidelines_02/APPENDIX_A.htm).

<sup>12</sup> For current NIH guidelines and proposed revisions, see [http://oba.od.nih.gov/rdna/nih\\_guidelines\\_oba.html](http://oba.od.nih.gov/rdna/nih_guidelines_oba.html), accessed on November 1, 2011.

<sup>13</sup> [http://oba.od.nih.gov/oba/rac/News/Section%20III-E-1\\_NewProposal.pdf](http://oba.od.nih.gov/oba/rac/News/Section%20III-E-1_NewProposal.pdf), accessed November 10, 2011.

<sup>14</sup> Unless otherwise noted information in this section came from: Environmental Protection Agency 40 CFR Parts 700, 720, 721, 723, and 725 Microbial Products of Biotechnology; Final Regulation Under the Toxic Substances Control Act; Final Rule. April, 11, 1997. <http://www.epa.gov/fedrgstr/EPA-TOX/1997/April/Day-11/t8669.pdf>

<sup>15</sup> Defined as “those microorganisms formed by deliberate combinations of genetic material from organisms classified in different taxonomic genera” at the United States Regulatory Agencies Unified Biotechnology Website: <http://usbiotechreg.nbii.gov/roles.asp>.

intending to “manufacture, import, or process” microorganisms for commercial purposes is required to file either a Microbial Commercial Activity Notice (MCAN) or a TSCA Experimental Release Application (TERA) which are used when a specific test involving release of the microorganism into the environment is planned. MCAN’s must be filed with the EPA at least 90 days before use of the microbe at which time the EPA has 90 days to review the submission in order to determine whether the new microorganism may present an unreasonable risk to human health or the environment. Research that is conducted without a connection to commercial funding and is in compliance with the NIH guidelines does not require a MCAN be filed but does require a TERA application if the researcher plans to conduct a field test.<sup>17</sup> TERA applications must be filed with the EPA at least 60 days prior to initiating field trials.<sup>18</sup> “Commercial Purposes” are defined to include any activities “with the purpose of obtaining an immediate or eventual commercial advantage for the manufacturer, importer, or processor” and covers the usage of “any amount of a microorganism or microbial mixture”. Commercial distribution, including test marketing, product research, and development of an intermediate are also covered by these regulations.

Notably, the regulations also apply to “substances that are produced coincidentally during the manufacture, processing, use, or disposal of another microorganism or microbial mixture, including byproducts that are separated from [it]...and impurities that remain in [it].” Furthermore “mobile genetic elements”, defined as any “element of genetic material that has the ability to move genetic material within and between organisms... Includ[ing] all plasmids, viruses, transposons, insertion sequences, and other classes of elements with these general properties” are regulated as well.<sup>19</sup>

Entities making MCAN or TERA submissions to the EPA under these regulations are required to submit information allowing the microorganism to be “accurately and unambiguously identified”, including taxonomic designations “for the donor organism and the recipient microorganism to the level of strain, as appropriate. These designations must be substantiated by a letter from a culture collection, literature references, or the results of tests conducted for the purpose of taxonomic classification.” The submitting entity is furthermore required to provide, upon the EPA’s request, data supporting the taxonomic designation, including “the genetic history of the recipient microorganism...documented back to the isolate from which it was derived.”<sup>20</sup> Submitters are moreover directed to provide “supplemental” information incorporating both phenotypic<sup>21</sup> and genotypic<sup>22</sup> information.<sup>23</sup>

As with the NIH guidelines, the EPA regulations have also introduced certain exemptions. These exemptions apply to experiments regulated by other federal agencies and those contained within a structure such as a greenhouse<sup>24</sup> if researchers maintain records demonstrating eligibility. Most academic researchers are exempt from this record keeping requirement provided their institution is in compliance with NIH Guidelines for Research Involving Recombinant DNA Molecules. Likewise, the EPA has determined some organisms to be associated with low risk with respect to the characteristics of the recipients. These organisms are eligible for Tier I or Tier II exemptions given the users certify that they meet certain eligibility requirements. To qualify for an exemption, research must be conducted using one of the ten recipient microorganisms listed as exempt and the genetic material must meet certain criteria for toxicity, stability, and poor mobilization. Furthermore, the researcher must certify they meet containment procedures, including killing the microorganism. If exempt there is no review by the EPA; the manufacturer need only certify that they meet these requirements.<sup>25</sup> This exemption is most commonly used by manufactures of specialty and commodity chemicals, particularly industrial enzymes.<sup>26</sup> “These exemptions

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<sup>16</sup> Interview with Thomas Crosetto of EPA TSCA Region 5 (IL,IN,MI,MN,OH,WI), July 26, 2007.

<sup>17</sup> Personal communication with Jim Alwood, Chemical Control Division, EPA. February 19, 2008.

<sup>18</sup> 40 CFR § 725.1

<sup>19</sup> 40 CFR § 725.3

<sup>20</sup> 40 CFR § 725.12 (a)

<sup>21</sup> Phenotypic information is defined as “pertinent traits that result from the interaction of a microorganism’s genotype and the environment in which it is intended to be used and may include intentionally added biochemical and physiological traits”. 40 CFR § 725.12 (b) (1)

<sup>22</sup> Genotypic information is defined as “the pertinent and distinguishing genotypic characteristics of a microorganism, such as the identity of the introduced genetic material and the methods used to construct the reported microorganism. This also may include information on the vector construct, the cellular location, and the number of copies of the introduced genetic material.” 40 CFR § 725.12 (b) (2)

<sup>23</sup> 40 CFR § 725.12 (b)

<sup>24</sup> In personal communications with Jim Alwood, Chemical Control Division, EPA. February 19, 2008, it was stated that a greenhouse is not considered to be acceptable for containment of microbes.

<sup>25</sup> Personal communication with Jim Alwood, Chemical Control Division, EPA. February 22, 2008.

<sup>26</sup> FACT SHEET Microbial Products of Biotechnology: Final Regulations Under the Toxic Substances Control Act. <http://www.epa.gov/oppt/biotech/pubs/pdf/fs-002.pdf>

could be very relevant to synthetic biology. Any manufacturer who inserts synthetic DNA into one of the eligible microorganisms and meets other criteria could use this exemption instead of an MCAN.”<sup>27</sup>

In addition to commercial microbes, the EPA also regulates pesticides, including genetically engineered pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). EPA notes “With regard to biotechnology, EPA’s jurisdiction under FIFRA covers regulation of the new substance and DNA in the plant when it is pesticidal in nature”<sup>28</sup> such as the introduction of gene that codes for the toxin from *Bacillus thuringiensis* into maize. Researchers wishing to gather data necessary to grant registration under Section 3 of FIFRA for a pesticide not registered with the Agency or a new use of a registered pesticide may apply for an Experimental Use Permit. Within 120 days of receiving the application and all supporting data the EPA must grant or deny the application.<sup>29</sup> Before a pesticide can be marketed in the United States, the EPA must evaluate the product for possible risks to human health, risks to non-target organisms and environment, potential for gene flow and the need for insect resistance management plans

**Applicability and Enforcement of EPA Regulations:** The EPA conducts both regularly scheduled and surprise inspections of MCAN and TERA-filing companies. According to interviews with EPA officials, the agency currently employs approximately 30 inspectors each in four of the EPA TSCA Biotechnology program’s 10 regional offices (2, 4, 5, and 8).<sup>30,31</sup> Every MCAN or TERA-filing company has been inspected at least once. Inspections however, are restricted by statute (15 U.S.C. § 2610) from extending to “financial data, sales data (other than shipment data), pricing data, personnel data, or research data” (other than data required to verify compliance). In the event that violations are discovered in the course of an inspection, companies may be subject to civil penalties of up to \$25,000 for each violation of the regulations.<sup>32</sup> Note that there is no assurance that non-registered facilities are in compliance as these facilities are not subject to inspection. Although this regulation covers many research activities performed using private funding, if research is conducted without a connection to commercial funding and is in compliance with the NIH guidelines, the EPA only needs to be involved if the researcher plans to conduct a field test.<sup>33</sup>

## **B. US Department of Agriculture –Animal and Plant Health Inspection Service**<sup>34</sup>

The Animal and Plant Health Inspection Service (APHIS) of the USDA regulates the introduction (importation, interstate movement, and release into the environment) of genetically engineered organisms (including plants, insects, or microbes) that may pose a risk to plant or animal health. Depending on the plant, introduction may require an APHIS permit or APHIS notification.

Notification is a streamlined version of the permit process but cannot be used for the introduction of all modified plants, nor can it be used for other introduction of other organisms regulated by APHIS. To make use of the notification procedure the release must be fully terminated in one year and plants being introduced must meet the eligibility criteria listed in Table 3. Furthermore, introduction must be in accordance with all six specified performance standards found in Table 4. If the plant does not meet the criteria for notification, or if the engineered organism is not a plant, the applicant must follow the full permitting process. Note that some industrial research in synthetic biology involving the introduction of a plant, animal or insect would require full permitting because it does not meet the third criterion for exemption from notification: “The introduced genetic material does not produce an infectious or toxic entity or encode products intended for pharmaceutical or industrial use.”<sup>35</sup>

The permit process is similar to the notification process however more detailed information such as how the field tests will be performed, and how the organism will be moved may be required. APHIS reviews the information provided in the permit application to ensure that the organism will not pose harm to the surrounding

<sup>27</sup> Personal communication with Jim Alwood, Chemical Control Division, EPA. February 22,2008.

<sup>28</sup> U.S. Environmental Protection Agency: EPA’s Regulations of Biotechnology for Use in Pest Management. [http://www.epa.gov/pesticides/biopesticides/reg\\_of\\_biotech/eparegofbiotech.htm](http://www.epa.gov/pesticides/biopesticides/reg_of_biotech/eparegofbiotech.htm)

<sup>29</sup> Federal Insecticide, Fungicide, and Rodenticide Act [As Amended Through LL. 110-94, Enacted October 9, 200].

<sup>30</sup> Interview with Michael Bias, CBI Coordinator, EPA TSCA Region 2 (NJ, NY, PR, VI) on July 19, 2007.

<sup>31</sup> EPA TSCA Biotechnology Program Contacts (very out of date) are available here: <http://www.epa.gov/opptintr/biotech/pubs/biocontx.htm>

<sup>32</sup> 15 U.S.C. § 2615

<sup>33</sup> Personal communication with Jim Alwood, Chemical Control Division, EPA. February 19. 2008.

<sup>34</sup> Unless otherwise noted, information in this section was taken from United States Department of Agriculture Animal and Plant Health Inspection Service’s Biotechnology website: <http://www.aphis.usda.gov/biotechnology/index.shtml>.

<sup>35</sup> USDA’s Biotechnology Notification Process: Biotechnology Regulatory Services, March 2005 [http://168.68.129.70/lpa/pubs/fsheet\\_faq\\_notice/fs\\_brsbiotechnotif.html](http://168.68.129.70/lpa/pubs/fsheet_faq_notice/fs_brsbiotechnotif.html)

environment. If there is a “high risk for a new plant variety to outcross with a weedy relative,”<sup>36</sup> APHIS may not authorize a field test or may, in conjunction with granting a permit, impose additional regulations to ensure the organism is handled safely and is properly confined. When enough evidence exists that a modified organism does not pose any greater risk than an equivalent unmodified organism, APHIS may grant the organism an unregulated status. Once receiving this status the modified organism may be “introduced into the United States without any further APHIS regulatory oversight.”<sup>37</sup> APHIS does not regulate the use of contained transgenic organisms. The unauthorized or accidental release of such organisms violates APHIS regulations. It is the responsibility of the researcher to ensure that unauthorized releases do not occur; therefore, APHIS encourages anyone working with transgenic organisms to abide by the NIH guidelines or other similar protocols.<sup>38</sup>

Finally, the Federal courts have on occasion reversed USDA approvals of GM plants. For example, on August 15, 2010, a Federal court revoked USDA approval of Monsanto’s Roundup resistant GM sugar beets. The court ruled that USDA had failed to consider fully potential environmental risks of GM sugar beets, especially the risk of out-crossing through horizontal gene transfer. It is not surprising that the courts and regulatory agencies differ in weighting of risks under conditions of uncertainty and controversy.

**Applicability and Enforcement of APHIS Regulations:**<sup>39</sup> Compliance with APHIS regulation is sought via education and outreach to developers of genetically engineered organisms as well as through inspections of field sites. A percentage of Notification Fields are inspected annually. Moreover, all permitted fields are inspected at least once and pharmaceutical and industrial field tests are inspected up to seven times, including before and after a field trial. If the APHIS inspector concludes that the test field does not meet standards immediate corrective actions must be taken. While minor infractions may be corrected without disturbing the test plot, serious incidents (such as unauthorized or accidental releases) may require “destruction of research plots, quarantine of harvested crops, formal corrective action plans, or other long-term measures.” Serious infractions or record of several small incidents, may lead to an investigation by the APHIS’ Investigative and Enforcement Services (IES). Identification by IES of serious infractions may lead to civil penalties including fines up to \$500,000 and the possibility of criminal prosecution.

<b>Table 3: APHIS Notification Eligibility Criteria<sup>40</sup></b>
The recipient organism is not listed as a noxious weed nor considered by APHIS to be a weed in the area of release
The introduced genetic material is ‘stably integrated’ in the plant genome
The function of the introduced genetic material is known and its expression in the regulated organism does not result in plant disease
The introduced genetic material does not produce an infectious or toxic entity or encode products intended for pharmaceutical or industrial use
The introduction does not pose significant risk of creating new plant viruses
The plant has not been modified to contain sequences from human or animal pathogens

<b>Table 4: APHIS Notification Performance Standards<sup>41</sup></b>
Shipping and maintenance at destination should not lead to release of viable plant into the environment.
Caution must be taken to avoid inadvertently mixing the regulated plant with non-regulated plant materials of any species which are not part of the environmental release
Regulated plants and plant parts must be maintained in such a way that the identity of all material is known while it is in use, and the plant parts must be contained or devitalized when no longer in use.
No viable vector agents may be associated with the regulated plant.
At the conclusion of the field trial no regulated plants or offspring may persist in the environment.
Upon termination of the field test, no viable material shall remain which is likely to volunteer <sup>42</sup> in subsequent seasons, or volunteers must be managed to prevent persistence in the environment

<sup>36</sup> USDA’s Role in Federal Regulation of Biotechnology. Jan 10, 2006. <http://www.ncsl.org/programs/agri/biotechfinal.htm>

<sup>37</sup> United States Department of Agriculture Animal and Plant Health Inspection Service’s Biotechnology website: <http://www.aphis.usda.gov/biotechnology/submissions.shtml>

<sup>38</sup> USDA-APHIS Biotechnology Regulatory Services *User’s Guide*: Notification. Biotechnology Regulatory Services Animal and Plant Health Inspection Service United States Department of Agriculture. Riverdale, MD. Feb. 2008.

<sup>39</sup> Information in this section was taken from [http://www.aphis.usda.gov/biotechnology/compliance\\_main.shtml](http://www.aphis.usda.gov/biotechnology/compliance_main.shtml) unless otherwise noted.

<sup>40</sup> USDA’s Biotechnology Notification Process: Biotechnology Regulatory Services, March 2005 [http://168.68.129.70/lpa/pubs/fsheet\\_faq\\_notice/fs\\_brsbiotechnotif.html](http://168.68.129.70/lpa/pubs/fsheet_faq_notice/fs_brsbiotechnotif.html)

<sup>41</sup> USDA’s Biotechnology Notification Process: Biotechnology Regulatory Services, March 2005 [http://168.68.129.70/lpa/pubs/fsheet\\_faq\\_notice/fs\\_brsbiotechnotif.html](http://168.68.129.70/lpa/pubs/fsheet_faq_notice/fs_brsbiotechnotif.html)

<sup>42</sup> Volunteer plants result from natural propagation, as opposed to growing after being deliberately planted.

### **C. Food and Drug Administration**<sup>43</sup>

The FDA regulates all plant-derived foods and feeds, including those altered using recombinant DNA techniques. Unlike the EPA and APHIS which have unique regulations specifically designed to address the area of synthetic biology, the FDA regulates food items that may be made via synthetic biology within the existing framework of acts including those relating to the safety of food products derived from new plants and those relating to food additives.<sup>44</sup> “FDA recognizes that whether there is a change in the legal status of a food resulting from a particular rDNA modification depends almost entirely on the nature of the modification, and that not every modification accomplished with rDNA techniques will alter the legal status of the food.” Following this reasoning, the FDA does not require premarket approval for all foods developed using recombinant DNA technology. However development of the product often falls under the regulatory authority of APHIS or the EPA. Likewise, food developed using this technology does not, necessarily, require special labeling. If a substance added through recombinant DNA techniques does not differ from other approved additives no premarket food additive approval is required, although the product still must meet all safety regulations related to food products derived from new plants.

If the food produced through the use of recombinant DNA techniques “contain substances that are significantly different from, or are present in food at a significantly higher level than, counterpart substances historically consumed in food,”<sup>45</sup> the new substances may not be generally regarded as safe and may require regulation as a food additive. Furthermore the introduction of proteins that are potential allergens into foods where that particular allergen is not naturally found may require special labeling or be prohibited by the FDA.<sup>46</sup> Additionally the FDA is aided by the EPA when evaluating residual pesticides created through biotechnology in food and animal feed. The Federal Food, Drug, and Cosmetics Act requires EPA to set tolerances, or exemptions from tolerances, for the allowable residues of pesticides in food so as to ensure they do not pose a danger to human health.<sup>47</sup>

**Applicability and Enforcement of FDA Regulations:** Although not required for food products created using recombinant DNA technologies per se, the FDA has made available a consultation process that allows developers to “actively consult with the FDA regarding their new plant varieties.” It is the FDA’s belief that the developers of all rDNA food commercially marketed in the US should consult with the agency prior to marketing.

### **III. Department of Commerce Regulations**

The Department of Commerce, Bureau of Industry and Security, has licensing authority over dual-use items.<sup>48</sup> These regulations are based on the list developed by the Australia Group described in Part Four of this document<sup>49</sup> and are enforced under the same classification system in each member nation.

Of particular interest is the control of the export of genetic elements that “contain nucleic acid sequences associated with pathogenicity” as well as those that contain nucleic acids coding for any of the toxins or any sub-units of a toxin.<sup>50</sup> A strict interpretation of this law would require a license for the export of any oligonucleotides or synthetic genes that contain sequences associated with pathogenicity of organisms on the control list.

It is worth noting that unlike many other portions of the EAR, Export Control Classification Numbers (ECCN) governing the export of dangerous human, animal, and plant pathogens and toxins (along with the genetic material associated with them) remain in force regardless of the intended destination of the export. In other

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<sup>43</sup> Information in this section was taken from [www.fda.gov/OHRMS/DOCKETS/98fr/011801a.htm](http://www.fda.gov/OHRMS/DOCKETS/98fr/011801a.htm), Draft Guidance, “Foods Developed Through Biotechnology”, Jan 17, 2001.

<sup>44</sup> FDA’s Policy on Foods Derived From New Plant Varieties. <http://www.nal.usda.gov/pgdic/Probe/v2n3/fda.html>

<sup>45</sup> Premarket Notice Concerning Bioengineered Foods. January 18, 2001. <http://www.cfsan.fda.gov/~lrd/fr010118.html>

<sup>46</sup> Premarket Notice Concerning Bioengineered Foods. January 18, 2001. <http://www.cfsan.fda.gov/~lrd/fr010118.html>

<sup>47</sup> EPA’s Regulation of Biotechnology for Use in Pest Management. June 2003. [http://www.epa.gov/pesticides/biopesticides/reg\\_of\\_biotech/eparegofbiotech.htm](http://www.epa.gov/pesticides/biopesticides/reg_of_biotech/eparegofbiotech.htm)

<sup>48</sup> Dual-use biologicals controlled by Commerce under the Export Administration Act are listed under Export Control Classification Numbers (ECCNs) 1C351 (“Human and zoonotic pathogens and toxins”), 1C352 (“Animal pathogens”), 1C353 (“Genetic elements and genetically-modified organisms”), 1C354 (“Plant pathogens”) and, 1C360 (“Select agents not controlled under ECCN 1C351, 1C352, or 1C354) found in Supplement No. 1 to Part 774 of the Export Administration Regulations (EAR).

<sup>49</sup> “The Australia Group (AG) is an informal forum of countries which, through the harmonisation of export controls, seeks to ensure that exports do not contribute to the development of chemical or biological weapons.” The Australia Group. <http://www.australiagroup.net/en/index.html>

<sup>50</sup> These regulations are controlled by 1C351 a. to d., 1C352, 1C354, and 1C360, ECCN 1C353, Supplement No. 1 to Part 774 of the Export Administration Regulations.

words, exports to Canada, the EU, or Japan require that the exporter undergo the same licensing as if it intended to export to China or Saudi Arabia. Furthermore, Commerce Regulations covering biologicals (Category 1C) have no “Low Value Shipment” authorized.<sup>51</sup> That is, a shipment of pathogens or genetic material will fall under the regulations regardless of its value. For other controlled items, like manufacturing equipment, the item must be worth at least a certain value for Commerce Department Regulations to apply.

Furthermore, even if all exports of dual-use biologicals (such as genetic material “associated with pathogenicity” from ECCN-listed agents) were to immediately cease, the Department of Commerce would likely continue to exercise regulatory authority over many if not all synthetic biology research through its control over “deemed exports” of technology (broadly defined in this context to mean “specific information necessary for the ‘development,’ ‘production,’ or ‘use’ of a product” controlled under the EAR)<sup>52</sup> via the transfer of expertise to a non-resident foreign national (including those in the United States under H-1B work visas). As in the case of “physical” exports, the “exporter” is required to seek an export license. “Exporters” are exempted from this requirement if the technology transfer occurs in the course of “fundamental research” that is pursued without a specific practical aim or with the intention of publication in the scientific or academic literature.<sup>53</sup> However, research and development conducted by private corporations, or funded by corporations, in which the findings are reviewed with the intent of controlling the results to be released in the open literature are considered proprietary and are subject to the licensing requirement.<sup>54</sup> The law governing dual-use exports under Commerce expired in August 2001 and the regulations are now governed by an Emergency Powers Act.

**Applicability and Enforcement of Commerce Department Regulations:** The issuance of an export license from the Commerce Department requires the exporter to submit all relevant information on the item to be exported and the end user and the government to complete a thorough government review of proposed export in a timely manner. The review process is to be completed within 30 days of the agencies’ receipt of the export application for review. In practice, the licensing process typically takes from six to eight weeks.<sup>55</sup> Unless a license has been approved, the shipment of an item requiring such a license is illegal. The text of this rule implies that those involved in synthetic biology based businesses, such as companies that make and sell oligonucleotides, may violate this rule when they ship synthetic DNA from pathogens. Customs and Border Protection has primary responsibility for the investigation of export violations and will likely be the first to investigate when an item is found to lack the necessary paperwork. In addition the Office of Export Enforcement within the Department of Commerce, Bureau of Industry and Security may also investigate and file charges for an illegal export. In either case, criminal and or civil charges may be filed and could involve large fines, prison time and/or the denial of all export privileges.

Due to the number of export applications received by BIS (about 12,000 yearly), NPC has restricted their review to a few areas of concern such as exports to the People’s Republic of China. It is consequently difficult to imagine this review program being substantially extended to cover exports of dual-use biologicals such as synthetic nucleotides, total orders for which number in the tens of millions each year, even if the industry first determines which few percent of products exported match sequences from controlled pathogens.

Furthermore, informal discussions with some industrial and academic biologists, revealed that few, if any, have obtained an export license for the export of these dual use synthetic products. In fact, most scientists we interviewed had never heard of these regulations. Even if the Commerce Department were to enforce these regulations on biologicals, it would be nearly impossible for customs inspectors to identify an illicit package without destructive testing unless the shipper declares the contents accurately.

#### **IV. Select Agent Rules (SAR)**

Although not specifically aimed at regulating synthetic biology, the Select Agent Rules ((42 C.F.R. Part 73, 7 C.F.R. Part 331, and 9 C.F.R. Part 121)<sup>56</sup>) contain language that makes them applicable to the field. These regulations, published jointly by the US Departments of Health and Human Services (HHS) and Agriculture (USDA) in the

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<sup>51</sup> Joe Chuchla, former Director, Nuclear Technology Division, Bureau of Export Administration (now Bureau of Industry and Security), Department of Commerce, personal communication, September 19, 2007.

<sup>52</sup> <http://www.bis.doc.gov/DeemedExports/DeemedExportsFAQs.html#23>

<sup>53</sup> EAR Part 772, page 4

<sup>54</sup> <http://www.bis.doc.gov/DeemedExports/DeemedExportsFAQs.html#23>

<sup>55</sup> From conversations and correspondence with Joe Chuchla, former Director, Nuclear Technology Division, Bureau of Export Administration (now Bureau of Industry and Security), Department of Commerce, May 25, 2007 – June 11, 2007.

<sup>56</sup> [http://www.selectagents.gov/resources/42\\_cfr\\_73\\_final\\_rule.pdf](http://www.selectagents.gov/resources/42_cfr_73_final_rule.pdf)

Federal Register,<sup>57</sup> draw upon authority established by Congress through the Antiterrorism and Effective Death Penalty Act of 1996<sup>58</sup>, the USA PATRIOT (Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism) Act<sup>59</sup> of 2001, and the Public Health Security and Bioterrorism Preparedness and Response Act of 2002<sup>60</sup>. The primary goal of the Select Agent program is to regulate the possession, use, and transfer of a specified list of select agents and toxins<sup>61</sup> that are considered potentially severe risks to human, animal or plant health, or to animal or plant products. However, the rules also apply to “Genetic Elements, Recombinant Nucleic Acids, and Recombinant Organisms” derived from them. This formulation is subsequently defined as: “Nucleic acids that can produce infectious forms of any of the select agent viruses listed in paragraph (b) of [§ 73.3]”, “Recombinant nucleic acids that encode for the functional form(s) of any of the toxins listed...if the nucleic acids: Can be expressed *in vivo* or *in vitro*, or are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*”, and “select agents and toxins...that have been genetically modified.”<sup>62</sup> Consequently, it would appear that the Select Agent Rules are not intended to regulate the use, possession, or transfer of synthetic genetic fragments that are unable, by themselves to produce a functional form of a listed agent or toxin (such a DNA oligos or synthetic genes.) However synthetic biology technology used to create functional infectious agent or toxins appears to fall under the Select Agent Rules.

Section 73.18 of the Select Agent Rules confers upon the HHS Secretary the authority to order surprise inspections of the facilities and records of any registered entities (including the ability to copy any records relating to activities covered by these regulations), to ensure compliance with the Rules. HHS is further authorized to inspect and evaluate the premises and records of any entity applying for registration, prior to the issuance of a certificate of registration. According to recent correspondence with CDC officials, the CDC alone has conducted over 630 inspections since 2003 to ensure that entities are following appropriate safety and security measures, as spelled out in the regulations. All CDC-registered entities have been inspected at least once. In 2006, CDC conducted 242 inspections to register or re-register entities. Approximately 30 inspectors (both civil servants and contractors) are currently employed by the CDC Division of Select Agents and Toxins to perform these inspections.<sup>63</sup>

APHIS inspection procedures are similar to those of the CDC, though APHIS inspectors are not “centrally located within [the] Select Agent Program.”<sup>64</sup> While CDC inspectors are based within the CDC Select Agent Program and write the inspection reports as well as perform the inspections, the approximately 50 APHIS inspectors complete standard checklists and submit them to the APHIS Select Agent Program for review. The contents of these checklists are then incorporated into inspection reports generated within the APHIS Select Agent Program.

**Applicability and Enforcement of Select Agent Rules:** In the event that suspicion of a safety or security violation arises, whether in course of inspections, or by some other means (such as a tip), the regulatory authorities are able to apply administrative, civil, and/or criminal penalties upon violators. Upon revocation or suspension of a certificate of registration, the entity is required to “immediately stop all use of each select agent or toxin covered by the...order...safeguard and secure each select agent or toxin...from theft, loss, or release, and comply with all disposition instructions issued” by the relevant lead agency.<sup>65</sup> Regarding civil penalties, the Office of the Inspector General of the Department within HHS (and its analogue within USDA) is delegated authority to conduct investigations and to impose civil money penalties against any individual or entity for violations of the Select Agent Rules, as authorized by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. Civil penalties may be pursued in conjunction with criminal ones.

In the event that a suspicion of criminal misconduct arises on the part of CDC/APHIS or the Inspector s General of HHS and USDA, the case will be referred to relevant officials with the FBI.<sup>66</sup> Criminal penalties for

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<sup>57</sup> These regulations represent the “final rule”, superseding the “initial final rule” first promulgated in December 2002.

<sup>58</sup> <http://thomas.loc.gov/cgi-bin/query/z?c104:S.735.ENR>:

<sup>59</sup> <http://www.selectagents.gov/resources/USApatriotAct.pdf>

<sup>60</sup> <http://www.selectagents.gov/resources/PL107-188.pdf>

<sup>61</sup> Information is available at [www.selectagents.gov/resources/salist.pdf](http://www.selectagents.gov/resources/salist.pdf)

<sup>62</sup> 42 CFR Section 73.3

<sup>63</sup> From Correspondence with Lori Bane, Compliance Officer, CDC Division of Select Agents and Toxins, various dates.

<sup>64</sup> From Correspondence with Lori Bane, Compliance Officer, CDC Division of Select Agents and Toxins, August 6, 2007.

<sup>65</sup> 42 CFR § 73.8

<sup>66</sup> Should suspicion of criminal activity arise, CDC/APHIS would be expected to immediately suspend registration and to contact the FBI through a well-defined and robust liaison system. However, to the best knowledge of our contacts at the FBI WMD Directorate and the CDC Select

violations of the Select Agent regulations are defined under Title 18 Section 175b of the US Code. Possession without registration of a select agent or toxin is punishable by up to five years' imprisonment and/or a fine. Transfer to unregistered persons (if the transferor knows, or has reasonable cause to believe recipient is unregistered) is punishable by up to five years' imprisonment and/or fine.

Furthermore, the transport or shipment (excluding "duly authorized" US Government activity) of select agents or toxins via interstate or international commerce (or the receipt of select agents or toxins through interstate or international commerce) is punishable by up to 10 years' imprisonment and/or fine.<sup>67</sup> Section 175 of Title 18 of the US Code prescribes criminal penalties of fines and/or imprisonment for up to 10 years, for the possession of "any biological agent, toxin, or delivery system of a type or in a quantity that, under the circumstances, is not reasonably justified by a prophylactic, protective, bona fide research, or other peaceful purpose".<sup>68</sup> Possession of such materials for "use as a weapon" is, for its part, punishable by a fine, life imprisonment, or both.<sup>69</sup>

Although individuals and institutions registered to possess Select Agents appear to be well regulated, synthetic biology may allow non-registered persons access to these agents. Companies that produce custom DNA to order are urged under current law to determine what they are making or to screen who they are shipping the products to. The Select Agent rules do not apply to synthetic genetic fragments that are unable, by themselves to produce a functional form of a listed agent or toxin. However, possession of such synthetic fragments could allow unauthorized individuals to create prohibited microbes or toxins. Individuals doing so would be in violation of the Select Agent rule and would therefore be subject to criminal charges, if their activity was discovered.

#### **V. Screening Guidance for Providers of Synthetic Double-Stranded DNA**

On October 13, 2010, HHS published *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* in the Federal Register (Federal Register, Vol. 75, No. 197 2010). Following the guidance is voluntary, but it nonetheless provides insights into how the government could and might aim to limit risks to security in an age of synthetic biology. Under this guidance, providers of synthetic, double-stranded DNA accept two important responsibilities. First, they agree that they should know to whom they are distributing a product. Second, they should know whether the product they are synthesizing and distributing contains a "sequence of concern".

To achieve this, providers have agreed to conduct customer and sequence screening. The purpose of the customer screening is to establish the legitimacy of customers ordering synthetic double-stranded DNA sequences by verifying the identity and affiliation of customers and identifying any 'red flags' of which there is suspicion that the order could be used for inappropriate ends. Providers agree to check the customer against several lists of proscribed entities, such as the Department of Treasury Office of Foreign Asset Control list of Specifically Designated Nationals and Blocked Persons and the Department of Commerce Denied Persons List for domestic orders, and are required to follow the laws and regulations of US trade sanctions and export controls for international orders.

The purpose of the sequence screening is to identify whether "sequences of concern" are ordered. Sequences of concerns are defined as those that code for the select agents and toxins identified by CDC and APHIS in the Select Agent Regulations. If the complete sequence or unique parts of the sequences are identified, providers must make sure that customers have a certificate of registration from CDC or APHIS for using select agents or toxins. For international orders, providers should also screen for items on the Commerce Control List to ensure that they are in compliance with the Export Administration Regulations (EAR).

If either the customer or sequence screening cause concern, a follow-up screening must take place to verify the legitimacy of the customer and end-use of order. What a follow-up screening is to be composed of is less specific than for the two initial screening, but as far as possible, the identity, affiliation, and legitimacy of the customer must be obtained as well as the intended use of the ordered DNA. If the follow-up screening does not solve the concerns raised, the provider should contact the US Government, or more specifically either the FBI, the Select Agent Programs of CDC and APHIS or the Department of Commerce, for assistance and further action.

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Agent Division, suspicion of criminal misconduct has yet to arise in the course of CDC or APHIS investigations of Select Agent Rule violations. (From interviews and correspondence with Lori Bane of CDC and Tracy Rice of FBI).

<sup>67</sup> 18 U.S.C. § 175b

<sup>68</sup> 18 U.S.C. § 175 (b)

<sup>69</sup> 18 U.S.C. § 175 (c)

The viability of this voluntary agreement hinges on the relatively low cost of compliance with its terms and on the concentrated structure of the synthesis sector, with a relatively small number of relatively advanced firms doing most advanced synthesis. If advanced synthesis capabilities diffuse from a few firms to many and from firms to individuals, the effectiveness of voluntary codes of conduct will obviously decline.

## **EUROPEAN UNION DIRECTIVES AND REGULATIONS**

This section deals with the equivalent European Union (EU) regulations regarding Synthetic Biology. As in the US, regulations do not deal with synthetic biology *per se*. Typically, the processes and products of synthetic biology are covered by Directives and Regulations that deal with genetically modified organisms. The European regulations tend to be stricter than their US counterparts, especially with respect to labeling and traceability requirements. The more stringent European rules can be attributed to public concern about the potential dangers of genetically-modified organisms and food.

EU law is based on primary and secondary sources. Primary law lays down fundamental rules including the “Four Freedoms” of movement of goods, persons, services and capital across national borders and the division of power between the EU and 27 Member States.<sup>70</sup> Secondary law includes Directives and Regulations drafted by the European Commission and passed by the Council of Europe and the European Parliament. Member States must implement Directives by passing national laws that incorporate the Directive. Though legally binding, Directives leave some discretion to the Member State on interpretation and implementation. Some Member States copy the text of Directives into national laws without additional elaboration, while others craft national laws that incorporate, extend and interpret Directives in a manner deemed consistent with both EU Directives and national circumstances.

The enforcement of regulations, implemented directives and decisions is achieved through national administrative mechanisms applicable to the relevant national law. Therefore sanctions are set up by national authorities and enforced within the national legal systems. Sanctions might vary from country to country, as they can implement different enforcement mechanisms. Member States can choose from a wide variety of enforcement options to ensure that users comply with the regulations. These options include for example: providing advice, withdrawal of a given consent and prosecution. Regulations are addressed to the European public. Unlike directives, they are directly applicable without additional legal acts of the individual Member States.

The following section reviews EU Directives and samples national laws implementing the Directives. Because the applicability of Directives varies with national implementation, we include summaries of national experiences of Spain, Belgium, Estonia, the UK and Germany at the end of sections on the Directive on Contained Use of GMOs, the Directive on Deliberate Release of GMOs and the Directive on Liability.

### **I. Directive 90/219/EEC on Contained Use of Genetically Modified Micro-Organisms**<sup>71</sup>

The Directive regulates the contained use of genetically modified micro-organisms for research and industrial purposes. Directive 90/219/EEC has been amended several times to keep pace with evolving bio-technology.<sup>72</sup> In the EU a “genetically modified micro-organism” (GMM) is considered to be “a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination”. The Directive specifies three techniques through which genetic modification might occur: Recombinant nucleic acid techniques involving the formation of new combinations of genetic material; Techniques involving the direct introduction into a micro-organism of heritable material prepared outside the micro-organism, including micro-injection, macro-injection and micro-encapsulation; Cell fusion or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally. These techniques should be seen as mere examples; other techniques also lead to genetic modification and thus fall under the scope of the Directive.

The Directive defines contained use as “any operation in which micro-organisms are genetically modified or in which such genetically modified micro-organisms are cultured, stored, used, transported, destroyed or disposed of and for which 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”. The Directive does not apply to procedures which are not considered to result in genetic modification, including *in vitro* fertilisation; natural processes such as: conjugation, transduction, transformation; polyploidy induction, cell fusion; and to contained uses of Annex II

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<sup>70</sup> At the time of writing this guide, they included: Austria; Belgium; Bulgaria; Cyprus; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Luxembourg; Malta; Netherlands; Poland; Portugal; Romania; Slovakia; Slovenia; Spain; Sweden; United Kingdom

<sup>71</sup> Information on this Directive was taken from: [http://ec.europa.eu/health/files/eudralex/vol-1/dir\\_1990\\_219/dir\\_1990\\_219\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/dir_1990_219/dir_1990_219_en.pdf)

<sup>72</sup> Directive 98/81/EC: [http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/98\\_81/98\\_81\\_TC.html](http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/98_81/98_81_TC.html)

Commission Decision 2000/608/EC: [http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/2000\\_608/2000\\_608\\_T.html](http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/2000_608/2000_608_T.html)

Commission Decision 2005/174/EC: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:059:0020:0026:EN:PDF>

GMMs that are non-pathogenic, non-toxicogenic, non-allergenic GMMs that do not harbour known harmful adventitious agents that could cause harm to human health and the environment.

Prior to carrying out any contained use the user must assess potential risks posed to the environment and human health in the event that the GMMs were to escape, with special consideration paid to risks involved with the disposal of GMMs. Potentially harmful effects include: disease to humans, animals or plants; deleterious effects due to the impossibility of treating a disease or providing an effective prophylaxis; deleterious effects due to establishment or dissemination in the environment; deleterious effects due to the natural transfer of inserted genetic material to other organisms.

The Directive sets forth elements that must be taken account of during the risk assessment: (1) identification of any potentially harmful effects, in particular those associated with the recipient micro-organism, the genetic material inserted, the vector, the donor micro-organism, the resulting GMM; (2) the characteristics of the activity; (3) the severity of the potentially harmful effects; and (4) the likelihood of the potentially harmful effects being realized. The risk assessment process is divided into three steps. (1) The user must first identify harmful properties of the GMMs; (2) Based on this assessment the user must assign GMMs to one of four risk classes that correspond loosely to the four NIH risk levels; (3) Finally the user must take appropriate containment measures. Should the user have any doubts as to which risk class is appropriate, the user must apply the more stringent measures, unless the National Competent Authority (NCA) of the Member State has enough evidence that less stringent measures will suffice. To keep workplace and environmental exposure to any GMMs to the lowest practicable level, users are required to apply conventional lab safety measures, corresponding to the risk class of the contained use.<sup>73</sup> Additional requirements exist for activities with animals involving GMMs and for glasshouse/growth-room activities involving GMMs.<sup>74</sup> The risk assessment and the containment measures applied must be reviewed periodically. Should the assessment no longer be appropriate in the light of new scientific or technical knowledge it must be reassessed immediately. The same applies if the containment measures are no longer adequate.

Once risks have been assessed and the appropriate measures identified, the user must notify the NCA where the contained use is to take place. When premises will be used for contained uses for the first time, the user has to notify the NCA, regardless of the risk class of the proposed GMM. Amongst other information the user has to provide the following: address and general description of the premises; the name of the persons responsible for supervision and safety and information on their training and qualification; the identity and characteristics of the GMM; the risk class of the contained uses. The authority's consent for a certain premise and risk class covers the first use of that contained use and any contained use of a lower class. If a user wants to carry out a contained use of a higher risk class a new "first use" notification must be filed. Only after the authorities' consent has been obtained may the user proceed. If consent was given, the user is prohibited from altering the contained use, without conducting a new risk assessment and obtaining fresh consent. Once the "first-time" use has been granted in relation to class 1 contained uses, subsequent risk class 1 contained uses may proceed without further notification. Users of GMMs belonging to risk class 1 are merely required to keep records of each risk assessment, which must be presented to the NCA on request. Once the "first-time" use has been granted in relation to class 2 contained uses, subsequent risk class 2 contained use proposals must be sent to the NCA. The user may proceed with the contained use immediately after filing the new notification. Once the "first-time" use has been granted in relation to class 3 or class 4 contained uses, subsequent risk class 3 or 4 contained use proposals must be sent to the NCA. The user may only proceed with the contained use once the NCA has granted its approval.

Upon receipt of a "first-time" use proposal or a subsequent use proposal, the NCA must assess the proposal on four grounds: (1) the accuracy and completeness of the given information; (2) the correctness of the risk assessment; (3) the correctness of the designated risk class; and (4) the suitability of the containment measures. If necessary the NCA may request further information, ask the user to amend the designated risk class or modify the protective measurements. Until the user has complied with the authority's request, the authority can ask the user to suspend, terminate or hold off with the contained use. Where failure of the containment measures could lead to serious danger to humans and/or the environment an emergency plan must be drawn up. In case of an

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<sup>73</sup> [http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/98\\_81/98\\_81\\_A42.html#foot6](http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/98_81/98_81_A42.html#foot6)

<sup>74</sup> Containment and other protective measures for activities in animal units can be found at:

[http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/98\\_81/98\\_81\\_A44.html](http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/98_81/98_81_A44.html)

Containment and other protective measures for glasshouses and growth-rooms can be found at:

[http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/98\\_81/98\\_81\\_A43.html](http://www.biosafety.be/GB/Dir.Eur.GB/Cont.Use/98_81/98_81_A43.html)

accident the user has to inform the authorities immediately. He is required to specify the circumstances of the accident, the identity and quantities of the GMMs that got out and the measures taken. Member States must then take all necessary actions to curtail the outbreak and inform neighboring Member States that might be affected. The Directive provides for public consultation on proposed contained uses, if a Member State deems it necessary. This provision mostly applies to GMMs belonging to risk class 3 and 4. Enforcement procedures are taken up by the NCAs of each Member State. Almost all countries conduct regular inspections of the premises and inspectors can choose from a wide variety of enforcement options to ensure that users comply with the regulation. These options include providing advice, withdrawal of consent and prosecution.

#### **Applicability and Enforcement: National Implementation of Directive on Contained Use of GMMs**

The enforcement of EU regulations, directives and decisions is achieved through national administrative mechanisms applicable to relevant national law. National authorities set up sanctions and are imposed through national legal systems. Accordingly, sanctions vary from country to country. As the examples below drawn from five Member States suggest, Member States choose from a variety of enforcement options to ensure that users comply with the regulations.

**Spain:** Among the 27 EU Member States, Spain is considered as the most pro-GMO Member State. It is the only Member State within the EU where significant amounts of genetically modified crops are grown (about 25,000 hectares of GM maize).<sup>75</sup> As Spain failed to implement Directive 98/81/EC into national law in due time, the European Commission took Spain<sup>76</sup> to the European Court of Justice. The Court declared that by failing to adopt the laws and administrative provisions necessary to comply with the Directive, the Kingdom of Spain failed to fulfill its obligations under that directive and was thus ordered to pay the trial's cost.<sup>77</sup> In 2003 Spain finally implemented the Directive through the "GMO Act of 2003"<sup>78</sup> and two separate Decrees (one Decree implementing the procedural and technical requirements and one Decree addressing stakeholder involvement).

The "GMO Act of 2003" transposes the Directive on contained use as well as the Directive on Deliberate Release. The scope of the transposing legislation is extended to include the contained use of GM plants and animals. The definitions of GM, GMM and contained use are the same as the corresponding definitions in the Directives. Political power in Spain is channeled by a central government and 17 autonomous communities. Thus there are 18 competent authorities (CA) for contained uses; one on the national level and seventeen in the autonomous regions. Some autonomous regions have additional regional 'Bio-safety committees' that advise the regional CAs. Activities conducted by private sector companies and regional public research institutes are notified to the CAs of the autonomous regions, which coordinate with the National CA. Whereas activities conducted by the federal public research sector must be notified to the National CA, which coordinates with the CAs of the autonomous regions. In 2009 there were around 170 facilities that conducted contained use activities with GMOs.

Inspections are carried out before the authorization of an installation. They are conducted either by the autonomous regions or by the General State Administration, depending on the distribution of competence. During the inspection, the information provided by the notifier is verified and the containment measures are checked for their adequacy. If problems are detected, authorizations can be revoked or postponed until the problems are solved. In 2004 a minor accident occurred at the University of Navarre; a fire broke out in the air-conditioning system of a class 3 laboratory. At that time GMM cultures were stored in a freezer which did not incur any increase in temperature owing to the fire. After the fire, the CA of Navarre conducted an inspection and issued a report restricting the GMM activity to zones that had not been affected by the fire until the original state of the laboratory was restored.

**Belgium**<sup>79</sup>: The responsibility for implementing the Directive in Belgium is divided across Regional and Federal levels.<sup>80</sup> Belgium has separate statutes and competent authorities for each of three regions: the Brussels-Capital

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<sup>75</sup> <http://www.spectrezine.org/environment/gmo.htm>

<sup>76</sup> However, Spain was not the only Member State which failed to implement the Directive. The Commission also brought Belgium, Germany, the United Kingdom, Greece, Spain and Austria before the Court for failure to implement the Directive.

<sup>77</sup> <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/01/1202&format=HTML&aged=0&language=EN&guiLanguage=en>

<sup>78</sup> Law 9/2003 on contained use, deliberate release and commercialization of GMOs:

[http://www.mma.es/secciones/calidad\\_contaminacion/omg/legislacion\\_general/pdf/Lev\\_9\\_2003\\_.pdf](http://www.mma.es/secciones/calidad_contaminacion/omg/legislacion_general/pdf/Lev_9_2003_.pdf)

<sup>79</sup> All the information on Belgium was taken from: [http://www.biosafety.be/CU/PDF/Summary\\_report\\_EC\\_2009.pdf](http://www.biosafety.be/CU/PDF/Summary_report_EC_2009.pdf)

<sup>80</sup> The NCA on the federal level is the Scientific Institute of Public Health Biosafety and Biotechnology Unit (SBB) <https://www.wiv-isp.be/About-wiv-isp/Pages/FR-Introduction.aspx>

Region IBGE<sup>81</sup>; the Walloon Region DGRNE<sup>82</sup>; and the Flemish Region LNE<sup>83</sup>. In 2006-2009, 381 notifications were submitted to the Belgian NCAs. The majority of these notified GMMS belonged to risk class 1 or 2, a few GMMs belonged to risk class 3, and no notifications belonged to risk class 4. Of the 381 notifications, 275 were conducted for research purposes (eg. university research laboratories, and 77 were for commercial purposes (e.g. pharmaceutical companies). The rest was done for educational or diagnostic purposes. Belgian authorities reported difficulties with subsequent uses to the EU, with users erring in their risk evaluations of new or modified contained use. Between 2006-2009, 121 inspections were carried out on 28% of facilities performing contained use. There was significant variation in the percentage of firms inspected in each region, with 49 % in the Flemish Region, 19 % in the Brussels-Capital Region and 6 % in the Walloon Region. The inspectors sample pathogens and GMOs as a means to control the adequacy of containment and work practices. Problems encountered during inspections were: no regular supervision and control of the biosafety equipment, insufficient training and lack of biosafety procedures and incomplete registration of used and stored micro-organisms. Some facilities did not possess the requested environmental license or authorization for the concerned activities. Belgium's enforcement actions include summons on compliance with follow-ups and official reports of infringements. All three regional statutes require the user to submit certain information relating to risk classes 2, 3 and 4, so that the NCAs can establish external emergency plans. The user has to draw up an internal emergency plan, which must be submitted to the mayor. As of the end of 2009, no accidents have been reported in Belgium.

**Estonia.**<sup>84</sup> Estonia implemented the Directive in November 2001 through a national law called "geneetiliselt muundatud mikroorganismide seletud keskkonnas kasutamise seadus"<sup>85</sup>. Only a few contained uses have been carried out in Estonia, with the majority belonging to risk classes 1 and 2. The NCA in Estonia is the Labour Inspectorate.<sup>86</sup> All users are supposed to be inspected within one year after obtaining a license for contained uses. To date, inspectors have not detected any violations. Regarding the establishment of emergency plans, Estonia requires all users to establish accident and emergency plans. Through 2006 no accidents have been reported.

**United Kingdom.**<sup>87</sup> Great Britain implemented the Directive via the "The Genetically Modified Organisms (Contained Use) Regulations 2000" (S.I. 2000/2831)<sup>88</sup>. The scope of the Directive has been extended and also applies to the contained use of GM plants and animals. Northern Ireland has its own regulations, which are identical to the British regulations. Three NCAs are responsible for enforcement mechanisms: The Health and Safety Executive (HSE)<sup>89</sup> governs human health in England, Scotland and Wales; the Department for Environment, Food, Rural Affairs (DEFRA)<sup>90</sup> addresses environmental aspects in England and Wales; and the Scottish Government: addresses environmental aspects in Scotland.<sup>91</sup> The UK has more than 550 facilities conducting contained uses, the majority of which are located in Great Britain. Most contained uses are conducted in the public research sector. The majority of all contained uses belonged to lower risk classes, though contained uses with GMMs belonging to risk class 4 have been conducted. During 2004 and 2006 four accidents were notified in Great Britain, with GMM vaccinia virus, M.Tuberculosis and E Coli. The UK carries out frequent inspections prioritized using a rating system, which takes into account a number of criteria including: class of GMM; confidence in the management systems; time since the last inspection; issues arising from notification. If inspections reveal shortcomings, enforcement measures may range from providing written advice, through prohibition notices, to

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<sup>81</sup> **Regional Legislation:** Decree of the Government of the Brussels-Capital Region of 8 November 2001 [http://www.biosafety.be/CU/ArrRB01\\_FR/ArrRB01FR\\_TC.html](http://www.biosafety.be/CU/ArrRB01_FR/ArrRB01FR_TC.html) (in French); **NCA:** Brussels Institute for Management on the Environment <http://www.ibgebim.be/>

<sup>82</sup> **Regional Legislation:** Decree of the Walloon Government of 4 July 2002 [http://www.biosafety.be/PDF/ArrRW02\\_FR.pdf](http://www.biosafety.be/PDF/ArrRW02_FR.pdf) (in French); **NCA:** Service Public de Wallonie <http://spw.wallonie.be>

<sup>83</sup> **Regional Legislation:** Decree of the Flemish Government of 6 February 2002 [http://www.biosafety.be/PDF/BesVG04\\_FR.pdf](http://www.biosafety.be/PDF/BesVG04_FR.pdf) (in French); **NCA:** Vlaamse Minister van Leefmilieu; Departement Leefmilieu, Natuur en Energie <http://www.lne.be/>

<sup>84</sup> All the information on Estonia was taken from: [http://ec.europa.eu/food/food/biotechnology/reports\\_studies/docs/SEC\\_2007\\_1636\\_en.pdf](http://ec.europa.eu/food/food/biotechnology/reports_studies/docs/SEC_2007_1636_en.pdf)

<sup>85</sup> Contained Use of Genetically Modified Micro-Organisms Act <http://osha.europa.eu/fop/estonia/en/legislation/gmm-act.stm>

<sup>86</sup> Estonian Labour Inspectorate <http://www.ti.ee/index.php?page=10&>

<sup>87</sup> Information on the UK was taken from <http://www.hse.gov.uk/biosafety/gmo/uk3yearlyreport.pdf> and the "Survey on the implementation of Directive 2009/41/EC regulations in Europe on the contained use of genetically modified organisms" from Ameco Environmental Services (Ameco)

<sup>88</sup> Available at <http://www.legislation.gov.uk/uksi/2000/2831/contents/made>

<sup>89</sup> More Informations about the HSE: <http://www.hse.gov.uk/>

<sup>90</sup> Defra: <http://www.defra.gov.uk/>

<sup>91</sup> The Scottish Government: <http://home.scotland.gov.uk/home>

withdrawal of approval and prosecution. The UK has urged the Commission to exclude certain GMMs from the scope of the Directive as Art. 3 of the Directive allows for the exemption of certain GMMs from the scope of the Directive, once they are deemed safe for the human health and the environment. However, so far no GMMs have been taken through this procedure. The UK asked the Commission to approve of exemptions to reduce regulatory burdens and promote biotechnology.

**Germany:** The Genetic Engineering Law (GenTG)<sup>92</sup> regulates contained uses of GMMs, GM plants and GM animals. Competent Authorities (CAs) are established at the regional level: each of the 16 Bundesländer (Regions) has one CA which receives notifications and issues consent. On the federal level the “Federal Office for Consumer Protection and Food Safety” (BVL) advises regional CAs on issues relating to bio-safety.<sup>93</sup> GMMs under the GenTG are assigned to four risk classes. Class 3 or 4 organisms require public consultation prior to contained use. Each institute or company working with GMMs must appoint a responsible Biosafety Officer. Emergency plans and accidents are regulated under the Genetic Engineering Emergency Plan Ordinance (Gentechnik-Notfallverordnung),<sup>94</sup> and all facilities must set up internal emergency plans. In case of an accident, every Region is required to inform the BLV about the incident. Every Region develops its own inspection plan, with priorities set according to risk level. Risk class 1 and 2 activities are inspected once every three years and class 3 and class 4 activities are inspected every year. Inspections include checks of logbooks and, in individual cases, the check of GMO samples. In case of deficiencies in organizational or safety measures, approvals can be suspended or revoked.

## **II. Directive 2001/18/EC on Deliberate Release into the Environment of GMMs**<sup>95</sup>

This Directive regulates the 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 the general population and environment. It differentiates between Part B releases for experimental purposes that are controlled directly by the applicant and Part C releases that make GMOs available to third parties, whether for payment or free of charge. Part B releases require the approval of Member States where the GMO is to be released. Part C releases require approval of EU authorities as well as the Member State. This Directive does not cover GMOs produced using mutagenesis and cell fusion, and release associated with the transport of GMMs by road, rail, sea, air and inland waterways. Neither does it apply to genetically modified food and feed, which are governed by other specialized Directives. The Directive on deliberate release is based on the precautionary principle. It stipulates that if there is substantial doubt as to whether the release of a GMO will cause harm to the environment or to public health its release should not be approved.

**Part B on Deliberate Experimental Release:** Prior to release, users must conduct a thorough environmental risk assessment (ERA) and secure Member State approval. The ERA must assess immediate and delayed direct and indirect effects on human health or the environment. “Direct effects” refer to effects caused by the GMO itself and “indirect effects” refer to effects occurring through interaction of the GMO with other organisms or transfer of genetic material. “Immediate effects” refer to direct or indirect effects observed during the period of the release of the GMO and “Delayed effects” refer to direct or indirect effects that may become apparent at a later stage or after termination of the release. The ERA is to compare adverse effects of the GMO relative to those presented by the non-modified organism. In conducting the ERA, the user is required:<sup>96</sup> (1) To identify effects on disease, toxic and allergenicity; on genetic diversity and population dynamics in environment; on prophylactic or therapeutic treatments through transfer of genes conferring resistance to antibiotics used in human or veterinary medicine; (2) To evaluate the potential likelihood and consequences of each adverse effect; (3) To estimate the risk posed by each identified characteristic of the GMO; (4) To define a risk management strategy to address severe risks; (5) and to determine the overall risks posed by the GMO. If new information on effects of the GMO on human health or the environment becomes available, the ERA must be revised. In addition to the ERA, applicant notifications must include a technical dossier supplying information on personnel and training; interactions between the GMO and the environment; control, remediation methods, waste treatment and emergency response plans. On receipt of a

<sup>92</sup> <http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf> (German only)

<sup>93</sup> Information about the BVL is available at [http://www.bvl.bund.de/EN/Home/homepage\\_node.html](http://www.bvl.bund.de/EN/Home/homepage_node.html)

<sup>94</sup> Available at [www.gesetze-im-internet.de/bundesrecht/gentnotfv/gesamt.pdf](http://www.gesetze-im-internet.de/bundesrecht/gentnotfv/gesamt.pdf) (German only)

<sup>95</sup> Information on this Directive was taken from: [http://www.biosafety.be/GB/Dir.Eur.GB/Del.Rel./2001\\_18/2001\\_18\\_TC.html](http://www.biosafety.be/GB/Dir.Eur.GB/Del.Rel./2001_18/2001_18_TC.html)

<sup>96</sup> The Annex of the Directive explains these steps in great detail: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:106:0001:0038:EN:PDF>

notification, national authorities have 90 days to consult with the public as they deem appropriate and to either give consent (with or without conditions) or reject the proposal. Modifications of approved plans which could have consequences for human health and the environment must be notified to the NCA, and NCAs may require the user to suspend, modify or terminate the deliberate release.

**Part C on Deliberate Commercial Release:** These provisions apply to the deliberate release of GMO products to any third parties including release onto the market. The procedure for a Part C release is similar to a Part B release, but requires EU authorization as well as Member State approval. An approved Part C release can be marketed in all Member States. They may not prohibit, restrict or impede the placing on the market of GMOs as or in products which have been approved by the EU Commission unless a Member State receives new information regarding the safety of the GMO. The procedure for obtaining consent includes the following steps:

- (1) environmental risk assessment (as discussed above),
- (2) technical dossier including monitoring and reporting methods once the product has been released;
- (3) notification of the NCA where the GMO will be marketed first, with detailed information on conditions of use and handling, plans for monitoring, and proposals for labeling.

The NCA then has to publish an assessment report with conditions for approval or disapproval, which will be forwarded to the Commission. The Commission then deliberates with the other Member States and may also consult the public and relevant scientific and regulatory committees to form its opinion. The EU Commission's and NCA's final consent is given for a maximum of 10 years with provisions for renewal. After consent for a Part C release has been obtained, the user may release the product onto the market. Member States may not prohibit, restrict or impede the placing on the market of GMOs as or in products once consent has been given. However, there is one exception to this rule. If a Member State has sufficient reason to believe that a GMO, which has been properly released under this Directive constitutes a risk to human health or the environment, that Member State may provisionally restrict or prohibit the use and/or sale of that GMO on its territory. At the same time the Member State must inform the Commission and other Member States of its actions for joint consultation and decision. Following placement on the market, the user must ensure that monitoring and reporting are carried out in accord with conditions specified in the consent. The reports of this monitoring must be submitted to the Commission and the NCA of the Member State. If new information becomes available regarding the risks of the GMO to human health or the environment after the consent has been given, the user must immediately take the measures necessary to protect human health and the environment and inform the NCA. Member States are required to enact penalties for infringements and to take all necessary measures to ensure that they are implemented. The Directive merely states that these penalties must be effective, proportionate and dissuasive, but leaves details to Member States. Judicially, the Commission has the authority to grant authorization to the release of GMOs even if individual Member States disagree, but in practice the Commission has been reluctant to do so (Bernauer 2003).

The possibility for dead-lock between EU and national authorities is apparent. To decrease the potential for dead-lock the Commission agreed on an amendment to Directive 2001/18/EC that will give Member States full responsibility over cultivation within their territory. The Commission describes it as a proposal for combination of the EU science-based authorization system with freedom for Member States to decide on the cultivation of GMOs. In effect, member states are allowed to block authorization on grounds other than those based on a scientific assessment of health and environmental risks, such as effects for local agricultural systems and other social and economic impacts. The amendments must be approved by the European Parliament and the Council before entering into force (European Commission 2010), and this was not done as of May 2011.

**Applicability and Enforcement -- National Implementation of the Directive on Deliberate Release of GMMs:**

The vast majority of GMOs released in the EU to date have been released in Spain. The majority of Member States have either not received any applications for Deliberate Release (e.g. Austria, Ireland and Luxembourg, Slovenia, Cyprus), have received just a few (Finland, Italy, Belgium), or have denied all applications (e.g. Denmark).

**Spain:** Spain implemented Directive 2001/18 on April 25, 2003 by passing the "GMO Act of 2003". The CA for any new GM variety intended for commercial use is the Inter-ministerial Council for GMOs (CIOMG) which is assisted by the National Commission on Biosafety (*Comisión Nacional de Bioseguridad CNB*). Prior to every deliberate release of GMOs, the operator has to apply for an authorization. The application fee for Part B releases is 4525

Euros and for Part C releases it is 12.040 Euros.<sup>97</sup> To date there have been 405 plant environment releases in Spain.<sup>98</sup> Law 9/2003 also established fines for serious infringements and negligence of the law, such as the commercialization, import, export of GMOs without the prior authorization. Penalties include the suspension of the activity, the possible closure of facilities or fines up to 1,2 Mio. Euros.<sup>99</sup>

**Belgium:** Belgium transposed the Directive into national law in 2005.<sup>100</sup> The deliberate release of a GMO into the environment is prohibited unless written consent of the Competent Authority (CA) has been obtained. The CA grants consent based on the results of a scientific evaluation done by the “Biosafety Advisory Council” and based on the results of a 30-days public consultation process. Until 2006 Belgium received 3 Part B applications, two of which were approved and one was refused. The required fee for submission is 1250 Euros per Part B notification. For a Part C notification the fee ranges from 6200 Euros to 15.200 Euros . Three Part C applications were filed; two were refused and one was still pending.

**Estonia:** The Estonian legislation corresponding to the Directive is the “Deliberate Release into the Environment of Genetically Modified Organisms Act”.<sup>101</sup> The competent Authority is the Ministry of the Environment.<sup>102</sup> Neither Part B applications nor Part C applications have been filed until 2006. However, the fee for submitting a notification would be approximately 30 Euros.

**United Kingdom:** The UK incorporated the Directive into the “Genetically Modified Organisms (Deliberate Release) Regulations 2002”.<sup>103</sup> Directive 2001/18/EC has not led to any significant changes in what was required in the risk assessment. The UK already had very stringent regulations, regarding indirect or delayed effects in place. Nine Part B applications have been filed and all of them have been given consent. The fee for submitting a Part B notification is 5000 Pounds, whereas the fee for a Part C notification is 12.000 Pounds. The UK received three part C applications; one was denied and the other two were still pending. Non-industry stakeholders in the UK still remain largely negative towards Part C authorizations even though the Directive introduced a 10 year time limit.

**Germany:** The corresponding German legislation is the “Genetic Engineering Act” (GenTG).<sup>104</sup> In Germany, Part B releases begin with the submission of the notification to the Federal Office of Consumer Protection and Food Safety (BVL), which is the NCA. The BVL then draws up a risk assessment based on the data supplied by the notifier, statements put forward by the Central Commission for Biological Safety (CCBS), public objections, and statements of the various federal states. Finally, the BVL decides on whether to approve the deliberate release and if so under which specific safety requirements. Until 2006 25 Part B applications (deliberate release other than release onto the market) have been filed, 21 of which were approved, 1 was refused and the remaining were still pending at the time the report was written. The notifier has to pay a fee to submit a notification which will range from 5000 Euros to 30.000 Euros depending on the size and effort required. Germany only had four Part C applications, all of which were still pending.

### **III. Regulation 1829/2003 on Genetically Modified Food and Feed**<sup>105</sup>

The Directive on the deliberate release concerned mostly plant seeds, such as maize kernels or GM rapeseeds. This Regulation on the other hand covers food/feed products that contain or consist of GMOs, such as ketchup or animal feeds containing GM maize. In order to protect human and animal health, food and feed consisting of, containing or produced from GMOs should only be placed onto the market after a scientific evaluation of the highest possible standard has been undertaken. The evaluation is done by the European Food Safety Authority (EFSA). The regulation covers food and feed produced “from” a GMO but not food and feed “with” a GMO. The determining criterion is whether or not material derived from the genetically modified source is present in the food or in the feed. Food and feed which are manufactured with the help of a genetically modified processing aid are not included in the scope of this Regulation. Therefore, products obtained from animals fed with genetically

<sup>97</sup> [http://www.saveourseeds.org/downloads/COM\\_report\\_releases\\_march2006.pdf?reference=IP/05/793&format=HTML&aged=0](http://www.saveourseeds.org/downloads/COM_report_releases_march2006.pdf?reference=IP/05/793&format=HTML&aged=0)

<sup>98</sup> <http://mbg.jrc.ec.europa.eu/deliberate/ES.asp>

<sup>99</sup> <http://technology.open.ac.uk/cts/national/spain%20national%20report%20PEG.pdf>, p.7

<sup>100</sup> Royal Decree of 21 February 2005, [http://www.biosafety.be/LF/AROGM\\_2005/AROGM\\_TC.html](http://www.biosafety.be/LF/AROGM_2005/AROGM_TC.html)

<sup>101</sup> <http://www.legaltext.ee/text/en/X90013.htm>

<sup>102</sup> <http://www.envir.ee/67244>

<sup>103</sup> <http://www.legislation.gov.uk/ukxi/2002/2443/contents/made>

<sup>104</sup> <http://www.gesetze-im-internet.de/gentg/> (German only)

<sup>105</sup> Information on this Regulation was taken from: <http://eur-lex.europa.eu/LexUriServ/site/en/consleg/2003/R/02003R1829-20070112-en.pdf>

modified feed will not be subject to this Regulation. Food, such as eggs, milk and meat produced from animals fed on GM feed (e.g. maize), also fall outside the scope of the Regulation concerning the traceability and labeling of GMOs. These products don't need to be labeled or traced.

The regulation introduced the so called "one door – one key" procedure for the scientific assessment and authorization of GMOs and GM food and feed. It puts in place a uniform EU procedure for all marketing applications, whether they concern the GMO itself or the food and feed products derived thereof. The user does not need to request separate authorizations for the use of the GMO, and for its use in feed or food. A GMO which has obtained authorization can be used not only in food and animal feed but also for cultivation or deliberate release into the environment. The Regulation applies to: GMOs for food and feed use (e.g. sweet corn); Food/feed containing or consisting of GMOs (e.g. cornstarch); Food/feed produced from or containing ingredients produced from GMOs (e.g. polenta made from cornstarch). According to Art. 4(1) the above mentioned food and feed must not: have adverse effects on human health, animal health or the environment; differ from the food which it is intended to replace to such an extent that its normal consumption would be nutritionally disadvantageous for the consumer; mislead the consumer.

The user applying for an authorization (and after the authorization is granted, the authorization-holder or his representative) must be residing in the EU. The role of the NCAs in each Member State is limited under this regulation, as a European body, namely the EFSA is introduced. Though the user has to send the notification to the NCA, it merely passes it on to the EFSA, which grants authorization subject to a single risk assessment process. The notification has to include the following: name and address of the applicant; designation of the food, and its specification including the transformation event(s) used; studies that demonstrate that the food complies with the criteria referred to in Article 4(1) [see above]; samples of the food; a proposal for post-market monitoring.

The EFSA has 6 months to give its opinion, during which it may ask national authorities to conduct an environmental risk assessment or to carry out a safety assessment of the food. If additional data is deemed necessary during the scientific assessment the time limit is extended. If the EFSA's opinion is in favor of authorizing the food, it may impose conditions or restrictions for placing the food on the market and/or for use and handling, including post-market monitoring requirements. The NCA has to forward its opinion to the European Commission, the Member States and the applicant. The EFSA also has to state the reasons for its opinion and the information on which this opinion is based. The Commission has 3 months to decide whether to grant an authorization or to deny it. If authorization is granted, it is valid throughout the Community for 10 years after which it must be renewed. The authorized food must be entered into a Register. Each food must be labeled (see below). In addition to the labeling requirements referred to below, the labeling should also mention the following: (1) if a food is different from its conventional counterpart as regards the following characteristics or properties:: composition; nutritional value or nutritional effects; intended use of the food; implications for the health of certain sections of the population; and (2) where a food may give rise to ethical or religious concerns, the label must indicate so.

#### **IV. Regulation 1830/2003 concerning the traceability and labeling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms**<sup>106</sup>

The following Regulation requires Member States to take measures to ensure traceability and labeling of authorized genetically modified organisms at all stages of their placing on the market (the Directive on the deliberate release into the environment of GMOs only mentioned the labeling, see above). Labeling requirements are necessary to ensure that consumers are fully informed about GMOs and the products, foods and feed produced from them, in order to allow them to make an informed choice of product. Traceability requirements are necessary to monitor potential harmful effects and to facilitate the withdrawal of products in case such adverse effects on human health, animal health or the environment have been detected.

The Regulation applies to: products consisting of, or containing, GMOs, placed on the market in accordance with EU legislation; food produced from GMOs, placed on the market in accordance with EU legislation; feed produced from GMOs, placed on the market in accordance with EU legislation.

The regulation applies to all stages of the placing onto the market. Excluded from its scope are medicinal products for human and veterinary use authorized under Regulation 2309/93/EEC.

Under this regulation "traceability" means the ability to trace GMOs and products produced from GMOs at all stages of their placing on the market through the production and distribution chains. In order to trace them

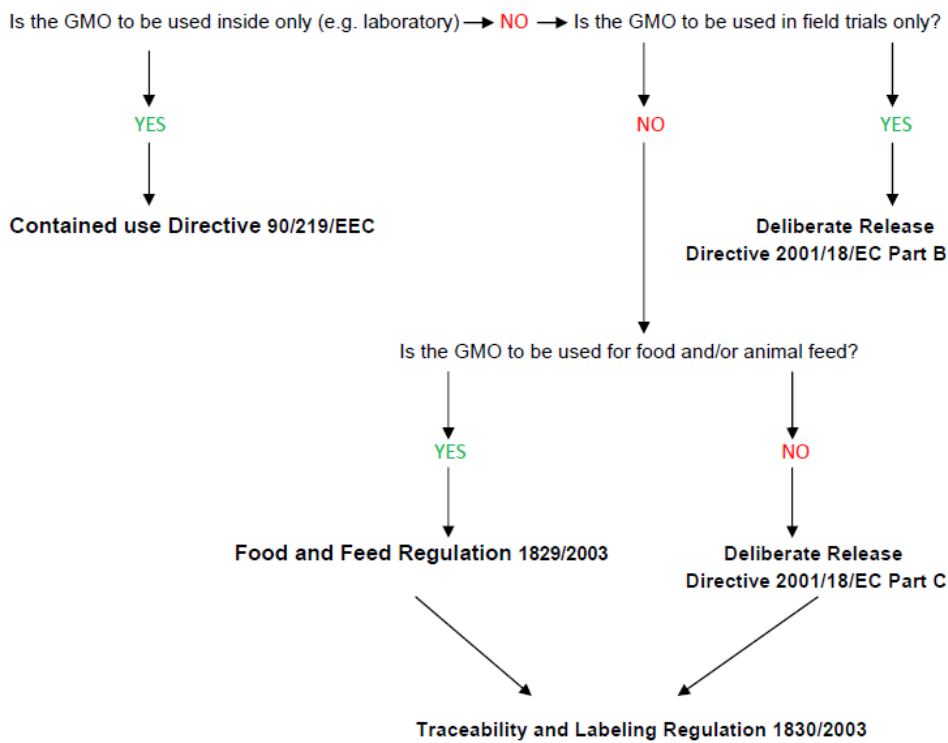
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<sup>106</sup> Information on this Regulation was taken from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0024:0028:EN:PDF>

all products are equipped with a “unique identifier”. A “unique identifier” refers to a simple numeric or alphanumeric code which serves to identify a GMO and to provide the means to retrieve specific information pertinent to that GMO. The codes may be used to access specific information on GMOs from a register, and to facilitate their identification, detection and monitoring. Products consisting of or containing GMOs must be marked with either one of these two sentences “This product contains genetically modified organisms” or “This product contains genetically modified [name of organism(s)]”. “Operators” are required to store information, concerning from whom and to whom products were supplied for at least five years. (“Operator” means a natural or legal person who places a product on the market or who receives a product that has been placed on the market in the EU, either from a Member State or from a third country, at any stage of the production and distribution chain, but does not include the final consumer.) In addition, they have to store the following information: an indication of each of the food ingredients which is produced from GMOs; an indication of each of the feed materials or additives which is produced from GMOs; in the case of products for which no list of ingredients exists, an indication that the product is produced from GMOs

Certain traces of GMOs in products may be adventitious or technically unavoidable. Such presence of GMOs does not trigger labeling and traceability requirements, if they are below certain thresholds. (E.g. the presence in food or feed of material which contains, consists of or is produced from GMOs in a proportion no higher than 0,9 % of all the food’s ingredients does not trigger these requirements). The Regulation urges Member States to lay down rules on penalties applicable to infringements of these provisions.

**Basic structure of the EU “GMO regulations”**



**V. Regulation 428/2009 on export controls of dual-use goods<sup>107</sup>**

Dual-use items are products and technologies that can be used for both civilian and military purposes including all kinds of goods to support the production of biological, chemical and atomic weapons. The export control regulations are stated in Council Regulation No 428/2009. The European Commission is a member of the Australia Group and of the Nuclear Suppliers Group. Therefore the EU list of controlled items is based on control lists adopted by international export control regimes.

<sup>107</sup> Information on this Regulation was taken from: [http://trade.ec.europa.eu/doclib/docs/2009/june/tradoc\\_143390.pdf](http://trade.ec.europa.eu/doclib/docs/2009/june/tradoc_143390.pdf)

Export in the sense of the aforementioned regulation means the transport of goods from an EU Member State to third countries. Every export of dual-use items to third countries requires an authorization, whereas the transportation between the EU Member States is free of border controls or other commercial restrictions. The export authorisation must be applied for in the EU Member State from which the dual-use items are to be transferred. Export authorisation granted by one Member State is valid throughout the EU. But every Member State may request another Member State not to grant authorisation or, if such authorisation has been granted, request its abrogation, amendment or revocation if the export may affect the State's essential security interests. Each EU Member State has to set up appropriate measures to ensure the enforcement of these provisions.

#### **VI. European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR)<sup>108</sup>**

The international transport of dangerous goods by road is governed by the European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR). The ADR sets up standards for the classification, packaging and equipment for the transport of dangerous goods. It also covers GMOs and GMMs, which are regarded as “environmentally hazardous substances”. They are assigned to class 9, which consists of “miscellaneous dangerous substances and articles” if they do not meet the definition of toxic or infectious substances; if they were to meet these definitions they would belong to a stricter class. In order to be eligible for transportation they must meet certain packaging requirements, listed in Art. 4.1.1.1.<sup>109</sup> These requirements stipulate that packages must be closed so as to prevent any loss of contents and no dangerous residue shall adhere to the outside of the packages. As long as goods, vehicles and drivers comply with this agreement, dangerous goods are able to cross international borders freely without further inspections.

#### **VII. EU legal framework concerning the prevention of bio-terrorist acts**

The level of attention given to bio terrorism in Europe is considerably lower than in the US. This explains why there is less regulation governing biological weapons. In November 2009 the Council of the European Union passed an Action Plan regarding the risks caused by unconventional weapons such as chemical, biological, radiological or nuclear (CBRN) weapons. It has to be pointed out that there is still no consistent definition of the term “biological weapon” in the EU legal framework. The Member States are obliged to amend their national legal framework with adequate descriptions of what is considered as a biological weapon. The EU CBRN Action Plan is part of the EU Counter Terrorism Strategy established in 2005. It is based on the findings of the CBRN Task Force which was asked to prepare a list of measures that could be taken up by the EU and the Member States to lower the risks of bio terrorist acts. The goal of the EU CBRN policy is to minimize the threat of CBRN incidents and to protect the public. The EU CBRN Action Plan is based on an all-hazard-approach that covers all, natural or man-made, accidental or deliberate kinds of CBRN hazards.

It is the responsibility of the Member States to protect its civilians against CBRN incidents. Therefore all policies established by the CBRN Action Plan should be developed in close consultation with NCAs. Article 1 lit (f) of the 2002 framework decision on combating terrorism requires Member States to criminalize the “manufacture, possession, acquisition, transport, supply or use of weapons, explosives or of nuclear, biological or chemical weapons, as well as research into, and development of, biological and chemical weapons” as terrorist acts.<sup>110</sup> “Terrorist acts” refer to actions with the intention to intimidate a population or to destabilize or destroy the fundamental political, constitutional, economic or social structures of a country or an international organization. To prevent CBRN threats, the Member States have to improve their cooperation and information exchange concerning high risk materials. Suspicious transactions and behavior have to be detected and reported. Over the last few years the European Police Office (Europol) collected various kinds of data relating to terrorist threats in each Member State and published it in the EU Terrorism Situation and Trend Report (TE-SAT) to make the public aware of the possible threats of bio terrorism. To ensure the Member States’ preparedness and capability to respond to CBRN threats, their emergency plans have to be improved constantly as well as their ability to set up countermeasures.

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<sup>108</sup> Information on this agreement was taken from: <http://www.unece.org/trans/danger/publi/adr/adr2011/11contentse.html>

<sup>109</sup> <http://www.unece.org/fileadmin/DAM/trans/danger/publi/adr/adr2011/English/Part4.pdf>

<sup>110</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:164:0003:0007:EN:PDF>

### **VIII. Directive 2004/35/EC on environmental liability with regard to the prevention and remedying of environmental damage (ELD)**

The Directive implements a framework for environmental liability based on the "polluter pays" principle. The ELD holds operators liable for environmental damages and "imminent threats of damage" caused by their business activities. Imminent threats of damage refer to "a sufficient likelihood that environmental damage will occur in the future". The liability's purpose is to induce operators to adopt measures and develop practices to minimize the risks of environmental damage, so that their potential financial liabilities are reduced. The Directive defines "environmental damage" as following:

- direct or indirect damage to the aquatic environment;
- direct or indirect damage to species and natural habitats;
- direct or indirect contamination of the land.

The ELD distinguishes between two distinct liability regimes. The first is strict liability-based and applies to specific operators mentioned in Annex III of the Directive.<sup>111</sup> These are, for instance, activities which discharge heavy metals into water or the air, waste management activities (including landfills and incinerators) and activities concerning GMOs and GMMs. Under this first regime, the operator may be held responsible even if he is not at fault. The second regime applies to all other occupational activities and is fault-based. This means that the operator will be held liable only if he is at fault or negligent. The Directive excludes from its scope any damage or imminent damage resulting from: armed conflict, natural disaster, nuclear risks or activities covered by the Treaty establishing the European Atomic Energy Community; national defense or international security activities; activities covered by the international conventions listed in Annex IV<sup>112</sup>.

If environmental damage has not yet occurred but the threat of such damage is imminent, the national competent authority (NCA) of each Member State will require the operator to take the necessary preventive measures. In case the operator fails in taking up the necessary preventive measures, the NCA may take these measures itself and recover the costs incurred at a later time.

If environmental damage has already occurred, the NCA will require the operator to take the necessary restorative measures. These measures have to be determined on the basis of the rules and principles set out in Annex II of the Directive.<sup>113</sup> Annex II of the ELD introduced the following remedial measures: Primary remediation: its purpose is to return the damaged natural resources to their original "baseline" condition; Complementary remediation: in case the "baseline" conditions cannot be achieved or are not cost-effective, similar resources must be created elsewhere (e.g. an alternative habitat must be created); Compensatory remediation: includes compensation for the time period, in which the damaged resource is unable to provide its pre-damaged function. This is a new concept in the EU. Thus, European insurers do not have much experience with claims relating to compensatory remediation. In addition, different remedies exist depending on the type of damage that occurred: for damage affecting land, the ELD requires that the land concerned be decontaminated until there is no longer any serious risk of negative impact on human health; for damage affecting water, protected species and natural habitats, the ELD requires restoration of the environment to how it was before it was damaged. Damaged natural resources or impaired services must be restored or replaced by identical, similar or equivalent natural resources or services. In case the operator fails to comply, the NCA may take these measures itself and recover the costs incurred at a later time.

The ELD does not oblige operators to take out a financial security, such as insurance, to cover their potential insolvency. Art 14 merely requires Member States to encourage operators to make use of such mechanisms and must promote the development of such services. Thus, it is up to each Member State to introduce financial security requirements. For instance Portugal, Bulgaria and Greece have introduced mandatory financial security systems, whereas Lithuania and Czech Republic are considering such mandatory financial systems.<sup>114</sup> However, the majority of the EU Member States rely upon a voluntary security scheme.

The ELD does not prevent Member States from enacting more stringent provisions in relation to the prevention and remedying of environmental damage. While some EU Member States have followed the scope of the ELD very closely, others have extended its scope (e.g. Denmark, Spain and Hungary). Another obstacle insurers have to face

<sup>111</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:143:0056:0075:EN:PDF>

<sup>112</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:143:0056:0075:EN:PDF>

<sup>113</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:143:0056:0075:EN:PDF>

<sup>114</sup> [http://www.willis.com/documents/publications/Services/Environmental/Alert\\_Compulsory\\_Financial\\_Assurance.pdf](http://www.willis.com/documents/publications/Services/Environmental/Alert_Compulsory_Financial_Assurance.pdf)

is the fact that within some EU Member States (e.g. Austria, Belgium and Germany) the responsibility for implementing the ELD into national law lies at a regional level. Austria, for instance, has nine provinces. Since each province may have a different definition of protected habitats or species, differences within national legislation are likely to occur. Thus, there is no harmonized liability system within a Member State, let alone in Europe. These issues pose significant challenges for the insurers as two of the most important prerequisites for insurability are absent, namely legal clarity and certainty. Though some insurance companies like AIG or Allianz already offer pan-European “master” policies for companies operating in different Member States.<sup>115</sup>

As the ELD was drawn up in 2004, the ELD-related insurance market is still rather small. Bernard Tettamanti of Swiss Re pointed out, that in order for an insurance company to provide cover, it is important to first assess the potential risks associated with a particular activity or company, the probability of damages and the amount of potential losses. However, for ELD-related insurance there is very little information available, especially in terms of probability of damages and amount of potential losses.<sup>116</sup> Therefore, insurers tend to exclude certain ELD-related liabilities from its cover. Limitations primarily relate to GMOs, GMMs, nuclear activities and the use of chemical or hazardous products. These activities include non-predictable risks. Hence insurers are reluctant to provide cover (e.g. EAGLE by Allianz, AXA Corporate Solutions)<sup>117</sup>. Many insurers also exclude gradual (non-sudden) environmental damage (e.g. gradual pollution). Many insurers limit their cover to damages stemming from pollution events only. Thus the number of insurance products covering non-pollution events, such as fire, drought or flood caused by industrial activities, is limited. In addition cover is often not available for “compensatory remediation”. Compensatory remediation was introduced by the ELD and refers to any type of compensation for the time period, in which the damaged resource is unable to provide its pre-damaged function. However, even though there might not be any insurance available for these kind of damages, other security mechanisms, such as letters of credit and bonds might be available. Many insurers provide cover for damages up to 25 mio. Euros. In some cases the limit may be lower or higher, depending on whether the insurance policy is backed by reinsurance. The foremost principle though is that ELD-related insurance cover depends on a company’s activity, size, risk factors, locations, etc. The actual premiums, limits and exclusions depend heavily on these factors. Another explanation for the limited growth of ELD insurance products is the lack of public awareness. Many operators wrongly consider their conventional general liability policies as sufficient and thus show little interest in ELD related insurance. Aggravated by the current financial crisis, operators concentrate on expenses that are strictly necessary. As the risk of environmental liability is often perceived low, its coverage is not considered a priority.

**Applicability and Enforcement:** Variations in the implementation of EU Directives are common practice. These variations stem from different legal systems and regulatory structures within Member States as well as varied political pressure brought upon the national regulators. Differences also arise from diverse cultural, political and socio-economic heritages. In the instance of the ELD, most western European countries have opted for a voluntary security scheme, while most central and eastern European (CEE) countries have introduced mandatory insurance systems. These different approaches might be motivated by the financial and economic power of each Member State. The ELD holds operators liable for environmental damages and “imminent threats of damage” caused by their business activities. However, what happens if the operator does not have the necessary financial means to cover the damages? It is ultimately the state and tax payers, who have to pay. Most CEE countries have significantly fewer resources than Western European countries. Thus, they shift the burden of paying for the damages incurred to insurance companies.

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<sup>115</sup> <http://www.agcs.allianz.com/insights/expert-risk-articles/environmental-liability/>

<sup>116</sup> [http://www.biohost.org/eld/docs/BIO\\_ELD\\_Minutes\\_Workshop.pdf](http://www.biohost.org/eld/docs/BIO_ELD_Minutes_Workshop.pdf)

<sup>117</sup> [http://ec.europa.eu/environment/legal/liability/pdf/eld\\_report.pdf](http://ec.europa.eu/environment/legal/liability/pdf/eld_report.pdf) p.42

## INTERNATIONAL CONVENTIONS AND AGREEMENTS

The US and EU have accepted obligations to protect biological diversity, biosafety and biosecurity as a party to international conventions and agreements. This section reviews major provisions of these agreements and discusses their potential relevance to the field of synthetic biology.

### **I. The Convention on Biological Diversity**

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The Convention on Biological Diversity is a legally binding international treaty that was opened for signature in the Earth Summit in Rio de Janeiro in June 1992 and entered into force on December 29, 1993. The United States has signed, but not ratified the Convention. The three main goals of The Convention on Biological Diversity are stated in Article 1:

- Conservation of biological diversity;
- Sustainable use of biological resources and diversity;
- Fair and equitable sharing of the benefits arising from genetic resources.

In order to achieve this, Contracting Parties are required to, amongst other things, develop and implement national strategies for the conservation and sustainable use of biological diversity, identify and monitor components of biological diversity important for its conservation and sustainable use, regulate or manage biological resources, establish a system of protected areas, promote the protection of ecosystems, and encourage the equitable sharing of benefits arising out of utilization of traditional knowledge. Further, developed countries are encouraged to cooperate with and share technical and scientific knowledge relevant to biological diversity with developing countries, and provide financial support for the implementation of the Convention by developing countries.

The Convention also discusses the development and use of biotechnology and genetic resources. It specifically requires Contracting Parties including the US to “[e]stablish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking into account the risks to human health.”

In relation to access to genetic resources, the Convention establishes that the authority to determine access to genetic resources rests with national governments and hence that access must rest on mutually agreed terms and subject to prior informed consent. Contracting Parties including the US are also required to take legislative, administrative or policy measures to provide for participation in biotechnological research, the fair and equitable sharing of results and benefits arising out of biotechnologies, especially with regard to developing countries who contribute with the genetic resources for such research. Parties also have to develop a protocol for the safe handling, transfer and use of living modified organisms.

### **II. The Cartagena Protocol on Biosafety and Nagoya-Kuala Lumpur Supplementary Protocol on Liability**

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The Cartagena Protocol provides a biosafety extension to the Convention of Biological Diversity. It was finalized and adopted in Montreal on January 29, 2000. To date, 159 countries and the European Union have ratified or acceded to it (United Nations 2010). Its objectives are stated in Article 1 as “to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, and specifically focusing on transboundary movements.” As such, it is intended to create a uniform international procedure for regulating the safe transfer of living modified organisms.

During the drafting of the Cartagena Protocol, negotiators differed over the question of whether it should address human health risks in addition to environmental risks (Street 2007). The current protocol contains references to human health and a specific section on GM food and feed, but these parts are weaker than those that address environmental risks. This is probably caused by the fact that governments view citizens and their well-being as more relevant constituents than the environment and are hence more reluctant to give up sovereignty in the politically more relevant area of human and public health than in environment.

The Cartagena Protocol only applies to international transboundary movement of living modified organisms for the intentional introduction into the environment of the importing Party; food, feed, and organisms designed for contained use are partially covered by the Protocol, but not as thoroughly as organisms for intentional release.

Living modified organisms are defined as any living organism that possesses a novel combination of genetic material obtained either through application of *in vitro* nucleic acid techniques (rDNA and direct injection of nucleic acids) or by fusion of cells beyond the taxonomic family.

Before exporting living modified organisms for intentional release into the environment exporters must notify the competent authority of the importing party in writing and submit specific information. The importer must perform a scientifically sound risk assessment based on the information submitted by the exporter, identify and evaluate the possible adverse effects of the modified organisms on the conservation and sustainable use of biological diversity, and make its decision based on this assessment.

The tension within the text regarding the grounds upon which parties may make decisions on the import of GMOs is interesting, especially since there were serious disagreements about the proper scope of the Protocol during the negotiations. The discussions about scope were centered on whether human health risks should be included, whether parties should be allowed to make decisions based on socio-economic factors and whether the precautionary principle should be allowed as a basis for decision-making (Street 2007). The issue of whether socio-economic considerations should be allowed as basis for decision making is unclear in the final text, where Article 26 allows for consideration of socio-economic factors while Article 10 requires decisions to be based on scientifically sound risk assessments. Furthermore, the phrase 'in consistence with their international obligations' included in Article 26 is a reference to their responsibilities under WTO agreements and thus an attempt to limit the ability of states to justify their decisions based on Article 26. Likewise, the precautionary principle is severely limited and may only be implemented if the scientific risk assessment is indecisive.

On October 12, 2010, parties to the Cartagena Protocol on Biosafety finalized six years of negotiations on a new treaty to establish international rules and procedures for liability and redress in case of damage to biological diversity resulting from living modified organisms (United Nations 2010). The "Nagoya-Luala Lumpur Supplementary Protocol on Liability and Redress" represents the first legally binding international rules for transboundary movements of living genetically modified organisms under the Cartagena Protocol.<sup>118</sup>

### **III. The Biological Weapons Convention**

The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and Their Destruction was opened for signature on April 10 1972 and entered into force on 26 March 1975. As of June 2005, 171 states had signed the convention, of which 16 still needed to ratify it, while 23 states had not signed (The Biological and Toxin Weapons Convention Wepage 2005). It supplements the Geneva Protocol of 1925, which only prohibits the use of chemical and biological weapons during warfare (League of Nations 1925) and is currently signed by 173 states.

Article I of The Biological Weapons Convention prohibits signatory states from developing, producing, stockpiling or otherwise acquiring or retaining "Microbial or other biological agents, or toxins whatever the origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes (and) Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purpose or in armed conflict." Subsequent articles require states to destroy or divert to peaceful purposes already existing biological agents and toxins, not to transfer or assist other state or non-state actors to manufacture or acquire biological agents and toxins, to take necessary measures to prevent development, production, stockpiling, acquisition or retention of agents within their own territory and to file complaints if it finds that another state violates the convention.

### **IV. The Australia Group Guidelines**

The Australia Group first met in 1985 and consisted of 15 countries. The meeting was prompted by the use of chemical weapons by Iraq in the Iran-Iraq war. Iraq had developed its chemical arsenal using tools and compounds legally purchased from Western nations.<sup>119</sup> The Australia Group formed to prevent Iraq from acquiring materials for the production of chemical weapons through otherwise legitimate trade through harmonization of

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<sup>118</sup>See GMO Compass 2010; and United Nations. "Press Release." *The Nagoya – Kuala Lumpur Protocol on Liability and Redress for Damage Resulting from Living Modified Organisms born in Nagoya*. Nagoya: United Nations, October 12, 2010.

<sup>119</sup> Rajiv Nayan, Australia Group, CBW Magazine. July 2008, Volume 1, Issue 4. [http://www.idsa.in/cbwmagazine/AustraliaGroup\\_rnayan\\_0708](http://www.idsa.in/cbwmagazine/AustraliaGroup_rnayan_0708)

national export controls. The Australia Group today is a collection of 41 countries<sup>120</sup> that have harmonized export controls over materials and technologies likely to contribute to the development of chemical or biological weapons.<sup>121</sup> The group provides a set of guidelines but has no enforcement mechanism. All Australia Group countries are signatories of the Chemical Weapons Convention and the Biological Weapons Convention, and “strongly support efforts under those Conventions to rid the world of Chemical and Biological Weapons.”<sup>122</sup> The group works by consensus, the agreement is non-binding, and all implementation takes place on the national level. It is important to note that the Australia Group is an informal arrangement that operates without the use of legally-binding obligations, relying heavily on the fact that all members are also members of the Biological Weapons Convention.

Biological agents and dual use biological technology were added to the Australia Group guidelines in 1992. The initial control list was published that year, and it has expanded greatly since.<sup>123</sup> In 2008, the group set up a synthetic biology advisory body to keep up with developments and to suggest responses to new innovations.<sup>124</sup> Currently, Australia Group guidelines relating to biological components cover dual-use technology, advanced software not available to an untrained user, and biological components that have pathogenic properties (bacteria, viruses, toxins, etc.). The guidelines also regulate: (1) Genetic elements containing nucleic acid sequences associated with the pathogenicity of any of the microorganisms on the control list. (2) Genetic elements containing nucleic acid sequences coding for any of the toxins in the list, or for their sub-units. (3) Genetically-modified organisms that contain nucleic acid sequences associated with the pathogenicity of any of the microorganisms in the list. (4) Genetically-modified organisms that contain nucleic acid sequences coding for any of the toxins in the list or for their sub-units.<sup>125</sup> The guidelines specify, “Genetically-modified organisms includes organisms in which the genetic material (nucleic acid sequences) has been altered in a way that does not occur naturally by mating and/or natural recombination, and encompasses those produced artificially in whole or in part. Genetic elements include inter alia chromosomes, genomes, plasmids, transposons, and vectors whether genetically modified or unmodified, or chemically synthesized in whole or in part.”<sup>126</sup> If the synthesized components do not code for part of a controlled pathogen or toxin, the guidelines do not apply. Also, if the genetic parts do not make up part of a genetic sequence that produces pathogenicity, then the components do not fall under the guidelines of the Australia Group, even if they do come from an organism on the control list. However, as new components are synthesized or isolated, their full functions within the DNA of a controlled pathogen may not be fully understood. This can lead to accidental shipments of components that have possible pathogenic properties.

As synthetic biology advances, more research will be performed on potentially dangerous organisms. Although the Australia Group has set up an advisory board to stay up to date with advances in the field, care must still be taken to ensure that potentially dangerous components are not moved across national boundaries inappropriately. A goal of synthetic biology is to create ways to more easily to modify organisms without advanced skills and equipment. This can allow untrained or even malicious actors to easily create a dangerous organism by assembling parts acquired from many sources. Due to these rapidly developing technologies, the guidelines laid down by the Australia Group are extremely relevant, and the group’s role in the international control of dangerous organisms should not be understated. The advisory body set up in 2008 should communicate often to keep up to date with this rapidly changing technology.

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<sup>120</sup> At the time of writing this guide, they included: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, European Union, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Republic of Korea, Latvia, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom, and the United States

<sup>121</sup> The Australia Group, Home, <http://www.australiagroup.net/en/index.html>

<sup>122</sup> Ibid, An introduction, <http://www.australiagroup.net/en/introduction.html>

<sup>123</sup> Rajiv Nayan, Australia Group, CBW Magazine. July 2008, Volume 1, Issue 4. [http://www.idsa.in/cbwmagazine/AustraliaGroup\\_rnayan\\_0708](http://www.idsa.in/cbwmagazine/AustraliaGroup_rnayan_0708)

<sup>124</sup> Ibid.

<sup>125</sup> Australia Group, Biological Agents for Control, [http://www.australiagroup.net/en/biological\\_agents.html](http://www.australiagroup.net/en/biological_agents.html)

<sup>126</sup> Ibid.

## **CONCLUSIONS: CURRENT COVERAGE AND FUTURE CONSIDERATIONS**

**Current Coverage:** How do US regulations and guidelines that bear on synthetic biology compare with EU Directives and regulations? In comparing US and EU standards that govern synthetic biology, it is important to examine both the letter of laws and their practical applicability. Levels of stringency for environment do not necessarily hold for security, practices in Western Europe do not necessarily hold for Eastern Europe, and practices within the US may vary from agency to agency while practices in the EU may vary from State to State and region to region within States.

As a first cut, relative to the US, the EU regulatory framework for approval of genetically engineered products for human consumption or environmental release addresses a broader range of biosafety risks with higher evidentiary standards. By contrast, with respect to biosecurity and synthetic biology, the postures of the US and EU reverse. US regulations of exports and domestic activities are more extensive and rigorously enforced than corresponding EU regulations. As discussed in the previous section, the EU and US have taken steps to implement international agreements bearing on biosecurity including the UN Bioweapons Convention and the Australia Group guidelines but significant gaps in coverage of the Bioweapons Convention and the voluntary nature and lack of specificity of Australia group guidelines are current sources of concern.

As Table 5 suggests, the US approach is premised on the assumption that regulation should focus not on production process *per se* but on the properties of products as regulated under existing statutes. Consequently, synthetic biology products are currently covered by three different US agencies operating under four separate statutes. The result is a regulatory system marked by fragmentation, lack of coordination and different standards for different types of products. For example, review of genetically modified animals that will not be used directly as food is more or less unregulated under the current framework, while genetically modified crops with plant incorporated protectants are nominally reviewed by all three agencies. Differences in statutory mandates, risk assessment methodologies and agency cultures between the EPA, APHIS and USDA create a system where the stringency of the risk assessment and approval process is more dependent on the specific product category than on the risk of the product. By contrast, EU regulations are premised on the assumption that distinctive regulations are needed to govern risks associated with recombinant DNA production methods.

In practice, differences between US and EU regulations of health and safety risks of synthetic biology may be more complex and difficult to characterize than the summary above suggests. Within the EU, national implementation of EU directives varies from nation to nation, with less rigorous regulation of Directives on contained applications and deliberate release in Spain or Estonia than in Germany or Denmark. The degree of funding of enforcement bodies and inspectorates also produces differences in effective levels of implementation. This can be seen quite clearly within as well as between countries. Belgium where the Flemish Region employed six inspectors, the Brussels-Capital Region two and the Walloon Region had no specialized inspectors at all.<sup>127</sup> Finally, it is important to mention that a given Directive may have different effects on Member States. In some countries the impact of the Directive is limited, for their national legislation has already met the requirements of the Directive (e.g. see the UK and the Directive on the deliberate release into the environment of GMOs). Other Member States like Estonia might implement national laws that just satisfy the minimum requirements of the Directive. By contrast, Belgium, has extended the scope of the Directive on the contained use of GMMs to include GMOs and non-GM human-, animal- and plant pathogens as well. Within the US, the rationale of the US government to not enact separate statutes for biotechnology has been undermined by specific regulations promulgated by responsible agencies. The US has, in effect, adopted on a piecemeal basis a regulatory system with separate review mechanisms for most biotechnological products like the European system. Finally, the degree to which current statutes, such as the TSCA, can be stretched to include and effectively handle technologies and products of synthetic biology remains unclear. Although individuals are responsible for living up to letter of the law, differences between formal requirements and informal implementation are often significant.

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<sup>127</sup> [http://www.biosafety.be/CU/PDF/Summary\\_report\\_EC\\_2009.pdf](http://www.biosafety.be/CU/PDF/Summary_report_EC_2009.pdf)

**Table 5: Analysis of regulatory coverage of safety and environmental risks of synthetic biology.**

Risk	International Regulation	US Regulation	EU Regulation
Transfer of genes	Cartagena Protocol on Biosafety	EPA & APHIS	Directive 2001/18/EC
Mutations, evolution and proliferation		EPA	Directive 2001/18/EC
Effects on ecosystem and other species	Cartagena Protocol on Biosafety	EPA & APHIS	Directive 2001/18/EC
Effects on biodiversity	Convention on Biological Diversity, Cartagena Protocol on Biosafety		Directive 2001/18/EC
Consumption risks		EPA (only for plant incorporated pesticides)	Regulation 1829/2003
Risks to laboratory workers		NIH Guidelines	Directive 2009/41/EC, Directive 2000/54/EC
Accidental release of laboratory strains		NIH Guidelines	Directive 2009/41/EC

Future Prospects: The regulations summarized above treat the use, sale and transport of synthetic biology products and processes. Many of these regulations are in their infancy. Where regulations exist, they often focus on the use of recombinant DNA or the transfer or use of microbes (or microbes derived from them) from set lists. That being said, synthetic biology challenges the utility of lists. Although it may seem like the height of sophistry, these laws do not define what *Bacillus anthracis* is and how it differs from *Bacillus cereus*. Both can cause illness in people (albeit *B. anthracis* causes more serious illness) so fall under the definition of a biological agent. Potentially, a researcher can modify *B. cereus* by adding into it all genes that *B. anthracis* has that *B. cereus* does not and deleting from it all genes that *B. cereus* has and *B. anthracis* does not. Since the genes from *B. anthracis* themselves are not regulated (not even the genes that encode anthrax toxins are listed, unlike in other toxogenic bacteria), and this modified organism isn't technically *derived* from *B. anthracis*, this organism probably would not be considered *B. anthracis* even if, after all manipulations, the final strain resembled *B. anthracis* more than any other organism. This situation becomes even more complex if the researcher was careful not to modify the *B. cereus* strain with *exact* copies of *B. anthracis* genes, but used modified genes that encoded the same amino acid sequence via a different DNA sequence. Although this example strains the boundaries of scientific possibility, similar experiments with viruses on the list (and their close relatives) can be achieved in several laboratories today. Some regulations depend on the behavior of the agent partially address this problem; for example, the NIH guidelines classify agents by their ability to cause disease in humans. For completely novel agents or for highly modified versions of existing agents it is difficult to determine their place on this list, especially for agents that cause disease only in humans.

Although the above discussion primarily pertains to those trying to subvert list-based controls, and not legitimate researchers, the action of government to prevent this subversion could lead to more burdensome regulations that may interfere with research in synthetic biology. For example, some commenters have suggested that viral select agents be defined by sharing a quantum of genetic information with (presumably canonical) viruses on the list. For example, one commenter on the Select Agent Rule suggested controlling any synthetic or natural piece of nucleic acid “comprising at least 15% of the genome of the select agent”.<sup>128</sup> The government wisely chose not to adopt this suggestion because it would regulate viral fragments found in several laboratories performing basic molecular investigations of viruses. Similar problems arose when the regulations attempted to produce a molecular definition of *variola major*.<sup>129</sup> Another proposal is to define an organism using a few genes that are potentially dangerous and regulating all organisms with these genes. This system too has flaws. We are not currently able to identify all genes associated with pathogenicity or how genes work together to cause harm. In many cases a gene that causes pathogenicity in “organism A” may be harmless when inserted into “organism B.” If organisms are defined by a few genes, it is likely that many harmless bacteria will be subject to regulation.

<sup>128</sup> Federal Register, Vol 70 No 52, p13298; March 18, 2005.

<sup>129</sup> Enserink, M. “Unnoticed amendment bans synthesis of smallpox virus” *Science* **307** (5715) 2005.

Furthermore, because a gene may only be recognized as being critical for pathogenicity after the writing of a rule, the rules must either be constantly updated or be quickly obsolete.

Further complicating the issue of regulation is the possibility of development of novel totally synthetic organisms. In May 2010, the J. Craig Venter Institute announced the stepwise creation of a synthetic bacterial chromosome based on *M. mycoides* and its transfer into *M. capricolum*, where it replaced native DNA. The synthetic cell began replicating and making new sets of proteins. The properties of the synthetic cell are almost identical to natural *M. mycoides*. Over the long term, similar approaches will be used to produce synthetic organisms of increasingly novel design.<sup>130</sup> Although at the time this manuscript was written, novel entirely synthetic organism has not been constructed, the possibility for creating such an organism exists. Regulation of organisms that do not yet exist is fraught with challenges. Should all unique synthetic organisms be regulated or only potentially dangerous organisms? How can one determine if a unique synthetic organism is dangerous? Because the introduction of any new organism into an existing ecosystem can have adverse effects on indigenous species, the introduction of even seemingly harmless synthetic organism into the environment merits scrutiny.

Artificiality poses many novel regulatory challenges. For example, synthetic organisms may possess the ability to transfer genetic material, assuming they have any that can be transferred, with non-synthetic organisms. Existing regulations governing release of GMOs in the US and the EU explicitly raise the potential for horizontal gene flow as a major consideration in assessment of risks of release. One approach to reducing risks of gene flow entails knocking out codons to create increasingly artificial versions of the microorganisms that serve as biological chassis for implanted pathways. The paradox? The increasing artificiality of microorganisms that is intended to limit gene flow also triggers more regulatory scrutiny. The problem of developing methods for appraising risks and benefits associated with increasing novelty has yet to be addressed.

Synthetic biology has great promise for curing diseases, creating fuels and solving countless other problems we currently face. Unfortunately, the improper or malicious use of such technology creates a need for regulation. One of the greatest challenges facing those who create such regulations will be weighing the costs and benefits of each rule and developing an effective enforcement system. Well crafted regulations should account for the changes synthetic biology will foster while not unduly hindering beneficial research. The field of synthetic biology and the assessment of associated benefits and risks characterized by rapid change, exceptional complexity and substantial uncertainty. The promotion of benefits and governance of risks will require the development of more adaptive systems of regulation with explicit recognition of uncertainty, with well defined plans to gather information that bears on policy relevant sources of uncertainty, and with clearly defined mechanisms for incorporating emerging information on the nature of benefits and risks into regulations, rules and guidelines. In short, designers of systems of regulation should take their lead from the qualities of the adaptive and evolving living systems that they seek to protect.<sup>131</sup>

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<sup>130</sup> <http://www.sciencemag.org/content/328/5981/958.full.pdf>

<sup>131</sup> For examples of adaptive approaches to risk governance in other domains, see "Planned Adaptation in Risk Regulation: An Initial Survey of U.S. Environmental, Health, and Safety Regulation," Lawrence McCray, Kenneth A. Oye and Arthur C. Petersen, *Technological Forecasting & Social Change*, Volume 77, Issue 6, July 2010, pp 951-959; and "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Licensing," Hans Georg Eichler, Kenneth A. Oye et al, *Nature Clinical Pharmacology and Therapeutics*, under review.