

dual use

A report by

iGEM Team Bielefeld-CeBiTec 2015



1. Introduction	1
2. Dual Use – Definitions	1
2.1 Legislative definition of “dual use”	1
2.2 Definitions by advisory boards or non governmental organizations	2
3. Rules and restrictions within the iGEM competition: Biosafety and biosecurity	4
4. Case studies of recent dual use dilemmas in the literature	6
5. Legal situation	7
5.1 Legal situation in the European Union	7
5.2 Legal situation in Germany	8
5.3 Legal situation in the United States of America.....	10
5.4 International regulations	12
5.5 Conclusions	13
6. Ethical questions.....	13
6.1 Freedom and responsibility in science	14
6.2 Responsibility of the researcher and call for supervision (Leopoldina).....	14
6.3 Responsibility of the publishing institutions	15
6.4 Responsibility of the government vs self-governance.....	16
6.5 Conclusions	17
7. Perspectives of biosecurity from the synthetic biology community.....	18
7.1 Conclusions	20
8. Proposed guidelines for minimizing risk of dual use	20
9. Can iGEM be a role model?	23
Publication bibliography.....	27

1. Introduction

Team Bielefeld-CeBiTec 2015 decided to propose an analysis of biosecurity, in detail the dual use issue, in the context of the iGEM competition. One aspect of this year's project of detecting date rape drugs ingredients, we found many cases of sensitive information to be published free for access on the internet. Especially the publication of ingredients and methods of synthesizing date rape drugs raised our concern. We discovered that chemicals that can be used as date rape drugs, are legally obtainable. In our opinion, this is knowledge that, in the wrong hands, can create a threat to the health of people. We were astonished how easy it is to obtain this knowledge and wondered if there are legal restrictions on the spreading of this knowledge. While we want to participate in an open source competition, we might ourselves provide sensitive knowledge on our homepage and wiki. During our collaboration, we spoke to teams dealing with similar problems. Since the iGEM competition encourages us to be striving to be conscientious members of the synthetic biology community, we want to complete this safety and security aspect by finding guidelines for the safe distribution of information and the question of dual use in research. Therefore, we chose not to restrict the analysis of the potential risk concerning the knowledge we might create and spread with our own project, but to analyze the legal situation with regard to publishing information with security concerns in general. By virtue of the diversity of laws in different countries, we focus on laws in Germany and the European Union that might affect us, as well as regulations in the United States of America, as the competition takes place there. We got in contact with several experts concerning legal and ethical questions, e.g. law students from another team, but also members of the federal office in Germany and the Ethics Council. While the term dual use is defined differently in Germany and the US, our focus is more the publication of information of any kind of research in journals, electronically and on paper, rather than the construction and export of dangerous materials and organisms itself, as the latter is already particularly described and regulated by legal institutions. We aim to analyze the current legal and ethical situation concerning dual use in general, well described cases of Dual Use Research of Concern (DURC), inform about the ethical dilemma of freedom of science versus oversight and restriction with the aim of providing security and strategies to minimize the risk of dual use in research in an open source context, as is the iGEM competition. Furthermore, we describe the potential of iGEM as a role model providing education and awareness on dual use concerns and the minimizing of its risks – for a better international collaboration to create beneficial knowledge.

2. Dual Use – Definitions

The term “dual use” has various meanings in different legal contexts as well as different nations. As the iGEM competition is international, but held in the United States of America, we want to focus on the US as well as Germany and the European Union, whose jurisdiction as a supranational legislative is explained in chapter 5.1, as our team's origin.

2.1 Legislative definition of “dual use”

German legal institutions understand dual use as the risk that chemicals, organisms or technologies can be misused for military purposes. “The foreign trade with commodities of strategic importance, mainly weapons, armaments and dual-use items, is subject to control. Dual-use items are goods, software and

technology that may be used for civil and military purposes. A milling machine, for example, may be used for processing components for civil as well as military products” (Federal Office for Economic Affairs and Export Control (Germany) 2015). Those goods are legally restricted in the context of production, provision and shipping. The European Union, which decrees binding laws as well as non binding proposals and guidelines to its member states, defines these dual use items very precisely in the so called dual use act. The list of “dual-use items” (European Union 2014) contains objects and technologies, such as information security, that are designed for or can be used for military purposes. A similar definition is documented at the U.S. department of commerce, Bureau of Industry and Security (BIS), that describes “Dual-use items subject to BIS regulatory jurisdiction have predominantly commercial uses, but also may have military applications” (Bureau of Industry and Security, U.S. Department of Commerce 2015).

Knowledge that might be used in both benevolent and malevolent ways is not specifically defined in these laws. Nevertheless, in the Netherlands a publication was considered a dual use item, as explained further in chapter 4 (Rechtbank Noord-Holland, of 9/20/2013). The definition anchored in the law is therefore, from our point of view, not sufficient for the state of art.

2.2 Definitions by advisory boards or non governmental organizations

Addressing the previously stated lack of definition by the legislatives, several non governmental organizations defined the term dual use. One of them is the Leopoldina, which is stated as the German National Academy of Sciences and hence represents the German research society. (Leopoldina - National Academy of Sciences 2015) The participating experts provide statements on current issues in collaboration with other organizations, like the DFG (German Research Society) and the German Ethics Council. All of these organizations deal with the context of research results creating knowledge with both beneficial and harmful potential and the question whether this concern requires ethical perspective and/or legal regulation. Just recently in 2014 a proposal regarding “Scientific Freedom and Scientific Responsibility – Recommendations for Handling Security-Relevant Research” (Deutsche Forschungsgesellschaft, Leopoldina 3/19/2010) and a discussion paper about the question whether benefits of research justify their potential risk (DFG / Leopoldina 2014) were published. Knowledge with both benevolent and malevolent potential is referred to as “security relevant research” in contrast to the dual use items in Germany.

The National Science Advisory Board (NSABB) is a federal advisory board of the United States Government and, on request of the government, addresses biosecurity and dual use research (National Science Advisory Board for Biosecurity 2015). The NSABB defines “dual use research of concern” as the “generation and communication of information and new technologies from life sciences research that have the potential for both benevolent and malevolent application (...) along with the subset of dual use research with significant potential for generating information that could be misused (...)”. (National Science Advisory Board for Biosecurity 2007) Dual Use Research of Concern is “Research that, based on current understanding, can be reasonably anticipated to provide knowledge, products or technologies that could be directly applied by others to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment or materiel”.

The Board agrees in general with an interpretation in a bulletin of the World Health Organization (WHO). The WHO is a non governmental organization acting on international level, which has many tasks. Among them the aim “to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products” and “to study, report on, in co-operation with other specialized agencies where necessary, administrative and social techniques affecting public health and medical care from preventive and curative points of view; including hospital services and social security.”. Therefore, as a matter of biosecurity, the WHO states “Scenarios where the results of well-intentioned scientific research can be used for both good and harmful purposes give rise to what is now widely known as the “dual-use dilemma” and there has been growing debate about the dual-use nature of life science research in particular” in its bulletin (Selgelid 2009). As task on the development of said standards, a Laboratory biosafety manual and biosecurity risk assessment were published. While we want to focus on the risk that publication of knowledge might contain, both definitions of dual use, an item of potential military use on the one hand and knowledge with potential misuse on the other, can not be separated strictly. While the National Advisory Board for Biosecurity deals with the dual use issue and the Leopoldina/DFG refers to the matter as security relevant research, the WHO defines biosecurity and biosafety as matters of materials and dual use as additional term:

Biosafety

“Laboratory biosafety describes the containment principles, technologies and practices that are implemented to prevent the unintentional exposure to pathogens and toxins, or their accidental release.”

(World Health Organization 2004)

Biosecurity

“Laboratory biosecurity describes the protection, control and accountability for valuable biological materials (...) within laboratories, in order to prevent their unauthorized access, loss, theft, misuse, diversion or intentional release.

Dual-Use

“Initially used to refer to the aspects of certain materials, information and technologies that are useful in both military and civilian spheres. The expression is increasingly being used to refer not only to military and civilian purposes, but also to harmful misuse and peaceful activities.” (World Health Organization 09 2006)

In view of these non consistent definitions in such an important field, we see the imperative of an international definition to establish a uniform basis for discussion and establishment of guidelines. Containing both definitions, namely the potential use of goods or technologies for military purposes as well as the potential misuse of information and knowledge, we find the definition of the WHO to fulfill those needs. Furthermore, we consider deliberate biosecurity to be not only the protection of material, but also the prevention of risks that arise by the knowledge provided in research.

3. Rules and restrictions within the iGEM competition: Biosafety and biosecurity

The crucial part of iGEM, regarding the wet lab part, is to handle molecular biological methods under the umbrella term of synthetic biology. Since every team is dealing not only with genetically modified organisms, but methods of synthetic biology to analyze, combine and build those organisms and DNA parts respectively, the question of regulation in context to biosecurity and biosafety is given. The question needs to be dealt with within each team and the competition itself as well.

However, definitions of biosafety and biosecurity are nowhere to be found within the iGEM safety page, while several instructional videos, regarding safe lab work and safe project design, are available. Safety forms need to be filled, concerning the organisms dealt with, proteins synthesized and various other questions. In our view, the questions asked are rather of biosafety concern than of biosecurity concern.

The members of the competition as well as the organizers of iGEM agree that all iGEM teams and their individual members are held to live up to the trust that is put into them by society and “design, build and share biological devices safely” (iGEM Safety Page). This includes safe project design. The question as to whether the designed product can be beneficial or harmful is one of the concerns of the project setup that should be asked at the very beginning of the development of the project: What will the product actually look like? Which impact will it have on society, economy and environment? Who will work with it? Where will it be used? What happens after it is used? To whom will it be beneficial or harmful? It is noticeable, that the questions asked try to cover a mixture of biosafety and biosecurity issues. The answers to these questions differ among the numerous iGEM projects in a very broad spectrum. Interestingly, all these questions aim to question the designed product or the used methods/chassis respectively, but not the information that is distributed among our society by the team’s homepages, wikis and public relations. Therefore the notion arises that these questions are mostly questions of biosafety rather than biosecurity.

In the following section, we will try to define biosafety and biosecurity aspects of the iGEM competition in more detail:

The aspect of safe lab work is very well defined. Organisms of the risk groups 3 and 4 as well as genes of those organisms are strictly prohibited within the competition. The danger they pose on the members as well as on the environment are considered too much of a risk to cover up the potential benefits obtained by possible iGEM projects. But also organisms of risk groups 1 and 2 are considered to be potentially harmful. Risk class 2 organisms require a check-in to avoid unnecessary risk and need to be replaced by organisms of risk class 1. Furthermore, the production of certain toxic proteins or genes of special risk, for example those enabling pathogens to act on the transcription and translation of their host, require the check-in and careful consideration of the potential benefits and harms. But also seemingly harmless organisms such as in risk group 1 might pose a risk. The idea of the iGEM competition and the parts registry is not only to improve existing parts, but also to design new devices by combining several existing BioBricks. By doing so, microorganisms obtain new characteristics and capabilities. Those can not only lead to the production of harmful substances by chance or accident, but can also transform potentially safe organisms into a threat, e.g. by increasing their potential of survival or mutations. General safety instructions for lab work are described in videos. Since iGEM is an

international competition that requires collaboration with other teams as well as the physical submission of DNA parts, shipping is an essential part to be considered. Struggling to take care of every country's legal situation of shipping DNA parts, genetically modified organisms or potentially harmful proteins and toxins, iGEM requires every team to take responsibility and gather information about its own and the collaborating team's national legal restrictions and/or regulations by the universities. In general, the liberation of genetically engineered microorganisms into the environment is strictly prohibited for the teams. Teams are encouraged to implement biosafety measures, such as kill switches, to avoid the spread in case of accidental release into the environment. With regards to these aspects, iGEM provided a list of organizations to obtain information from (iGEM Safety Page). In addition, participants are encouraged to contact the iGEM Safety Committee, which is a group of experts in biosafety, biosecurity and risk assessment. Any potential issue can and should be reported and discussed with the Committee.

Further, whereas biosafety is clearly outlined within questionnaires and check-ins for iGEM teams (iGEM Safety Page), we have found biosecurity to be a less specified topic. Aspects of dual use have found focus in Terry Johnson's call for awareness: iGEM participants, but also participants anywhere in the biotechnological environment, "should be aware of: the organization or organizations overseeing [ones] work, the appropriate Risk Group for the organisms that [one is] working with, and any select agents that might be involved. Further consider: any potentials for dual use, and especially if there are any biosafety or biosecurity concerns that are not addressed by current administrative controls" (Terry Johnson). We found potential biosecurity concerns within our project, like information about the date rape drugs (whose are part of our project), which are not yet addressed. Nevertheless, we have not found a guideline to address the concerns of publishing critical information. Hence, we want to provide these for a better and safer collaboration in the biotechnological community regarding the open source idea of the iGEM competition. In contrast to our findings this year, we were astonished to find biosecurity and potential misuse to be implemented in the 2011 iGEM Security Page. It states:

"As a participant in iGEM, there are three things you can do right now to help us secure our science:

1. Fully answer the safety questions that demonstrates that you have thought about how others could misuse your work
2. Contribute to community discussions on what needs to go into a code against the use of our science for hostile purposes (see A Community Response)
3. Look into what security provisions, such as laws and regulations, are already in place in your country (see Working within the Law)"

(iGEM 2011)

Since the answering of safety questions are obligatory, we addressed the additional proposals to contribute to a community discussion on what needs to go into a code with our proposal for the iGEM community. The consideration of laws and regulations is addressed as well in the sections law and ethics.

In consideration of the work of Team Leathbridge 2013, who analyzed threats by the artificial synthesis of potentially harmful gene sequences (iGEM Team Leathbridge 2013) and Team Peking 2010, who addressed the monitoring of horizontal gene transfer (iGEM Team Peking 2010), we want to acknowledge the work done on these critical aspects. They are examples of awareness of dangerous knowledge since it is the basis for the creation of sequences to be synthesized and the design of experiments containing horizontal gene transfer. Both analyses aim to describe the status quo of the dangerous action itself, not the monitoring of knowledge. Team Biohackers LA has addressed several aspects of federal and state restrictions and laws for operating with dangerous organisms and agents in the context of the do-it-yourself movement, yet they did not consider the information one is publishing within his project (iGEM Team LA Biohackers 2014).

Since the iGEM competition asks us to be “striving to be conscientious members of the synthetic biology community” (iGEM Safety Page), we want to complete this safety and security aspects by finding guidelines for the safe distribution of knowledge and the question of dual use research of concern. As it is an international competition aiming to promote the communication between researchers as well as between them and the public, iGEM could be a role model in considering the dual use dilemma. In section 8 we analyze the question of what has already been done and can be done in the future to fulfill that role.

4. Case studies of recent dual use dilemmas in the literature

We briefly describe five cases that caused a broad discussion about the benefits and risks of their publication. The last one actually inspired the recent debate about dual-use and many calls for establishment of institutional oversight. Many institutions and experts, such as the WHO, commented on these cases and recommended different, individual handling of every case in particular and dual use in general, yet no international laws exist that could apply to them.

- Jackson et al: Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox (Jackson et al. 2001)

Published in Journal of Virology in 2001, this research was aimed at creating a mutation of a mousepox virus, which would at the same time cause sterility of mice to control the infection. Surprisingly, it created a new strain of virus, which was able to kill even vaccinated mice. This technique is supposed to be applicable to smallpox that can infect humans as well. The only defense against smallpox is vaccination, as there is no known cure or therapy.

- Cello et al.: Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template (Cello et al. 2002)

In this publication researchers demonstrated that it is possible to create an artificial virus by combining chemically synthesized DNA fragments and adding proteins that are freely available. They prepared a cell extract containing the components necessary to convert the genome into an infective virus. The virus was able to infect and kill mice. A similar technique might be used to create bioweapons.

-Rosengard et al.: Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement (Rosengard et al. 2002)

One way in which a protein of the smallpox virus defeats the human immune system, was analyzed and described by mutating the gene encoding a similar but less virulent protein of the smallpox vaccine virus to mimic the smallpox protein gene sequence. Then it was demonstrated that this recombinant protein was as effective as the smallpox protein. With this knowledge, similar viruses could possibly be combined with these proteins, or new DNA sequences coding for such proteins, to increase their potential of infection.

- Tumpey et al.: Characterization of the reconstructed Influenza pandemic virus (Tumpey et al. 2005)

The virus that caused the Spanish Flu was recreated. This opened the possibility to develop medicine and cures for other influenza viruses, but the knowledge could also be used to recreate dangerous viruses for biological warfare.

- Fouchier et al.: Airborne transmission of influenza A/H5N1 virus between ferrets (Ron A.M. Fouchier 2012)

While aiming to provide knowledge for the creation of vaccinations, researchers published the development of airborne infection of ferrets. After their procedure, the virus, formerly not able to spread through the air between mammals, did become infectious over this route. In this case single members of the reviewing team disagreed on the question whether the benefits outweigh the risks. Nevertheless, the results were published (Robert Roos 2014). The case has been brought to court. It was decided, that the paper can be declared a dual-use item and therefore being regulated by export law.

In our opinion these cases clearly demonstrate the need for regular overview and international guidelines. The cases are handled differently in different countries of origin, yet all of them have an impact on global security and are discussed internationally. To provide an overview of possible applying laws, we further analyze the legal situation in the USA, the European Union and Germany as well as international regulation.

5. Legal situation

5.1 Legal situation in the European Union

The European Union is a union of several, yet not all European states. It provides European law that is binding for the member states (supranational legislative) as well as not binding proposals and guidelines. In the Europe Union, biosecurity-relevant research is considered in standard biosafety guidelines that are not binding. A special definition or applying binding law for the misuse of research information does not exist. Only the export of dual use goods to non-EU states is dealt with in the EU Dual Use-Act, which is declared as binding for the member states. (European Union 2014). Dual use goods may also include technology and software, so publications could be denied to be exported, when declared as technology. This happened in the Netherlands (Rechtbank Noord-Holland, of 9/20/2013), while several other publications, that were discussed for having dual use potential, were published without considering this law. Within the EU, the declaration of publications as export items is hence not consistent. Information about fundamental research as well as necessary information for patent filing are excluded from the act. For being declared as dual-use item, a general potential misuse of a good is not enough.

The European Commission, serving as the institution to provide implementations and amendments in oversight of existing laws for the EU, has recently called public consultation to a review of the export control policy, which is open until October 15th 2015 for general public. This consultation is aiming to be the basis for amendments of the Regulation (EC) N° 428/2009, which is currently applicable for dual-use concerns. The consultation has been called for various reasons. Among them are the potential risks created by the world wide web in general and the increased flow of information online as well as the fast development of new technologies:

- “Exports are increasingly transmitted, not transported. In the age of cloud computing, information flows containing sensitive technology can be used to produce unlimited quantities of sensitive goods and present a major challenge for export control, especially due to the inapplicability of border controls, and the difficulty for companies to ensure compliance (e.g. with respect to IT architecture, engineering collaboration, travel of experts etc.) (...)
- Scientific research leads to extraordinary advances that benefit society, but the risk that research could be misused creates a growing tension between the principle of openness in science and security concerns. Debates have highlighted the needs to take into consideration the nature of science and the free flow of scientific information, but have also emphasized the need to address the risk associated with potential abuse of scientific research and to ensure independent assessment of the security implications.” (European Union 2014)

While there is no guideline or legal restriction of the publication of sensitive information yet, these statements show awareness of the potential risk and the need of careful considerations of both openness and security. Hence, a change of the legal situation in the European Union regarding dual use research is expected after the submittal of the amendments. It states that “The Commission could examine options to promote a specific strategy to ensure “immaterial control” and address the challenge posed by Intangible Transfer of Technology (ITT). Further the amendment supposed to be including the need to clarify the control of “dual-use research”, while avoiding undue obstacles to the free flow of knowledge and the global competitiveness of EU science and technology” (European Union 2014).

5.2 Legal situation in Germany

The legal situation in Germany is bound to the agreements and laws of the European Union. In addition, the Basic Law of the Federal Republic of Germany and other laws apply. The freedom of science is granted under article 5 of the Basic Law:

“Article 5 [Freedom of expression, arts and sciences]

(1) Every person shall have the right freely to express and disseminate his opinions in speech, writing and pictures, and to inform himself without hindrance from generally accessible sources. Freedom of the press and freedom of reporting by means of broadcasts and films shall be guaranteed. There shall be no censorship.

(2) These rights shall find their limits in the provisions of general laws, in provisions for the protection of young persons, and in the right to personal honor.

(3) Arts and sciences, research and teaching shall be free. The freedom of teaching shall not release any person from allegiance to the constitution. “(Federal Republic of Germany 2012)

Research including any genetically engineered organisms underlies the GenTG (Gentechnikgesetz / “Genetic Engineering Act”) and GenTSV (Gentechnik-Sicherheitsverordnung / “Enactment of genetic safety”), which are the laws concerning any activity with genetically engineered organisms and the regulations concerning the safety of these researches. These works need to be registered and approved by governmental institutions. The Federal Office of consumer protection and food safety contains the ZKBS (zentrale Kommission für biologische Sicherheit). It states guidelines and information about the handling, registry and regulations of genetically modified organisms.

“The ZKBS assesses and controls the risks, that modification of the genes of an organism apply to humanity and environment. Therefore, it applies the GenTG and GenTSV. The question, if a research is concern of dual use potential, including the question if a genetically engineered organism or a technique can be misused for military purposes (or other intentionally malevolent purposes), is as of now not part of the work of the ZKBS and is not regulated by GenTG or GenTSV. Recently, the Leopoldina and the DFG assess this topic. In addition the federal office for economic affairs and export control and the dual use act EG-Dual Use VO No. 428/2009 apply. “



Federal Office of
consumer protection and food safety

Interview
with our team, 7th August, 2015

Thus, publications of fundamental research are free and are not governed by the dual use act. Hence, the DFG and the Leopoldina proposed guidelines. Although these guidelines cannot substitute a legal framework, all researchers are advised to reconsider these proposals. Both organizations approached researchers in their guidelines to not only consider the underlying law, but in case of ethical questions follow those guidelines for a safer research and minimizing risks for humanity (Deutsche Forschungsgesellschaft, Leopoldina 3/19/2010).

“The Leopoldina/DFG do not only consider biosecurity, but all kinds of security and safety relevant research. When analyzing possible measures for regulation of biosecurity



assessments, not only legal, but self-regulating measures were considered. The idea focusses on finding forms of research, which hold a balance between freedom of research and responsibility – within a defined legal framework. Therefore proposals were created, that consider the establishment of ethical committees at universities. Those committees can give advice to researchers as well as integrate biosecurity assessment in the education of young researchers. The idea is not only addressing single areas of research, but in general persons and organizations that conduct research and education.”

Prof. Alfons Bora, Leopoldina/DFG, University of Bielefeld (Sociology of Law)

5.3 Legal situation in the United States of America

Since 9/11 and the anthrax attacks in 2011, biosecurity is considered a national problem. The awareness of the potential risks of technology and research is very high. Two committees, the National Academies (Fink-commission) and the National Science Advisory Board for Biosecurity (NSABB) deal with the dual use research of concern and the potential misuse of information created in life sciences.

The “Proposed Framework of the Oversight of Dual Use Life Science: Strategies for Minimizing the Potential Misuse of Research Information”, provided by the NSABB as an advisory board for the US government, has exhibited insights and guidelines for the handling of the potential dual use risk. The NSABB proposed the creation of a regulatory framework for the oversight and handling of Dual Use Research of Concern (DURC). This proposal reaches out to every scientist to act responsible and attentive to potential misuse of his work (National Science Advisory Board for Biosecurity 2007). Nevertheless, the proposal has not been fully realized into a binding law up to now. Governmental funded research is screened, but the implementations proposed for research in general are not mandatory. E.g., only a few journals have integrated dual use in their review sheets. A study revealed that many editors indeed see a need for review for potential dual use, but only a minority of them are informed or experienced in this area of expertise (Daniel Patrone, David Resnik, Lisa Chin 2012). In addition, it is not required by law to check research for dual use potential. Similar to the legal situation in Germany and the European Union, biosafety regulations are anchored in the law, while biosecurity issues are rarely governed. Proposals concerning research involving genetically modified organisms and even double stranded DNA itself are reviewed by the ORA-IBC (Office of Research Administration - Institutional Biosafety Committee). Biosecurity concerns are affected by export regulations, but not by restrictions that address the publication of information. Soon the Office of Research Administration will launch the Institutional Review Entity (IRE) for dual use research of concern, which addresses this particular topic.

In addition, the National Academies of Sciences, Engineering and medicine provide expert advice for researchers and the government. A part of this institution, the National Research Council, is addressing

dual use issues. In 2004, a report was published on the risk of dual use research and its minimization, commonly known as Fink report or the “Biotechnology Research in an age of terrorism” report (National Research Council, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology 2004). It stated that an intensive training for scientists regarding dual use issues and biosecurity as well as biosafety is necessary and would help minimize the risk of dual use. The proposals have also not been realized. In 2012, federally funded research projects were screened for matters of dual use research of concern and grouped into seven categories. A “Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern” (DURC) in a three-step-examination was created, but it only applies to research of concern that is funded by United States Government (USG) inside and outside the United States, USG departments that fund these researches, and researches dealing with 15 certain agents or toxins, even if not funded by USG (United States Government). Other areas of the life sciences, even if dual use research is conducted, is not imposed by this policy (National Research Council, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology 2004). The U.S. government, similar as in the EU, does not apply binding laws for the research publication, if not governmentally funded, yet can influence the export:



"The U.S. Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern, which applies to United States Government funded or conducted research, “addresses institutional oversight of DURC, which includes policies, practices, and procedures to ensure DURC is identified and risk mitigation measures are implemented, where applicable.” (United States Government). The National Institute of Health has further promulgated its own policies through the National Science Advisory Board for Biosecurity (NSABB), a federal advisory committee established in 2005 that is tasked with providing advice to the U.S. government on biosecurity issues and dual use research. The

NSABB does not pre-approve the conduct of specific experiments or the publication of findings (U.S. Department of Health and Human Services 2015). At the request of the Secretary of the Department of Health and Human Services, however, the NSABB may review and provide guidance on experiments that involve a notable or novel category of dual use research or a particularly sensitive publication that may be considered dual use research of concern. While the above policies may not be binding, if an institution conducting DURC wishes to publish or transfer its findings, the information and tangible products derived from DURC may be subject to the United States export control system. “The Export Administration Act of 1979, as amended, authorizes the Department of Commerce, in consultation with other appropriate agencies, to regulate the export or re-export of U.S.-origin dual-use goods, software, and technology. The Department of Commerce implements this authority through the Export Administration Regulations (EAR).” (U.S. Government 2015). “

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5.4 International regulations

As a researcher with origin in the USA and experience in Germany, Prof. Nixdorff explained her view on international agreements in context with dual use at a symposium of the Leopoldina, DFG and German Ethics Council (DFG / Leopoldina 2014). She explained that the only comprehensive agreement on international level is the Biological Weapons Convention of 1972 (Federal Foreign Office (Germany)). In its general purpose criterion, it states:

“Article I

Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:

(1)

Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes;

(2)

Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.” (Russian Federation, United Kingdom of Great Britain, Northern Ireland and United States of America 3/26/1972)

Since 1972, research has made great progress and genetic engineering was established. Since the agreement is very open on which molecules are microbial or biological agents, also newly developed ones are covered by this convention, says Prof. Nixdorff. On the other hand it allows research for peaceful purposes. Nixdorff, as well as the German Federal Foreign Office (Federal Foreign Office (Germany)), point out a significant problem of the agreement: It contains various levels of agreements, ranging from binding for all members, over proposals, that should be implemented for political reasons, to not binding agreements on trust building measures. It lacks any institution of control of the actual implementation, not even on this highest level, the binding agreements. There are no means to determine if a member is in compliance and no provision for the oversight of dual use research. To ensure the inclusion of recent developments, additional agreements are postulated every 5 years in a Review Conference. One such agreement concerned submitting reports each year on activities relevant to the Convention (Confidence Building Measures), but according to Prof. Nixdorff only around 40% of the participating states are handing in their reports on the yearly basis. On an even lower level, common understandings are found. On this level many ideas and plans are formed, yet few of them are implemented in the single nations. In considering how the Convention might be strengthened at the level of compliance assurance, the call for establishment of a risk-management and an ethical codex for research concerning dual use can be found. It is considered a necessity to establish such a codex, because recent polls showed that most researches do not take potential dual use biosecurity risk into consideration in their work, says Nixdorff. Only the Netherlands and Italy have implemented a codex and can be understood as role models (DFG / Leopoldina 2014).

5.5 Conclusions

Considering the variation of the legal regulations and the lack of uniform interpretation of laws, we see the need for the implementation of guidelines on an international level. These guidelines do not need to be binding, but should implement a groundwork to build on the responsible and trustful interaction and collaborations of researchers worldwide. They could help to provide a greater awareness and better understanding of the dual use issue – towards a safer international research without the restriction of knowledge and progress.

We would like to point out the striking need for such guidelines in the research society. We would like to join researchers such as Prof. Nixdorff in their call for guidelines to establish the awareness of dual use, which we find essential for self-governance of research.



“At the international level, e.g. in context of the Biological Weapons Convention, a set of good practices in biosafety and biosecurity oversight should be identified and agreed upon by the States Parties to the Convention. These practices would guide the member states that have not yet done so in implementing internationally harmonized, relevant measures ensuring oversight of dual-use research of concern (DURC) at all institutions carrying out work in the life sciences and related fields at the national level. Not all of the same research oversight-governing measures can be implemented by all nations, due to different governmental systems and constitutions. However, certain basic elements should be agreed upon that can be

implemented by all nations carrying out relevant work, such as **awareness-raising measures** including education of all those working in relevant fields about dual-use biosecurity issues and the establishment of a national code of conduct; the implementation of **regulations** delineating the proper steps that the researchers should be required to take; measures specifically to establish comprehensive and coherent DURC oversight policy; and the establishment of a system of verification for the Biological Weapons Convention that can provide assurance that the States Parties are complying to the Convention.”

Prof. em. Kathryn Nixdorff

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6. Ethical questions

The discussion about moral and ethical questions of the dual use matter is of very broad range. The complete understanding of the ethical basis underlying the analysis lies far beyond a report of this size and our insights in ethics. We want to summarize our findings about the main ethical questions and contacted several experts in ethics, e.g. from the German Ethics Council, and advisors of these councils from Sociology and Law. During fruitful discussions we gathered insights in those different fields of

expertise and are able to provide a range of opinions from different points of views, also from outside of the laboratory. We provide an overview about several aspects commonly connected to synthetic biology, science with dual use potential in general and the possibilities of restrictions and oversight of these areas.

6.1 Freedom and responsibility in science

The modern world relies on research in various fields. The life sciences like chemistry, biochemistry, biotechnology and related areas are required for progress in technology, medicine, pharmaceuticals, diagnostics and fundamental research for a better understanding of plant, animal and human health. Therefore, they are necessary for improvement of our daily lives regarding nutrition, health, environment and comfort. Research in this area can thus not only be seen as beneficial for progress, but necessary. The research community is dependent on scientific communication and exchange of research result, in order to improve already existing knowledge. Further, the publication of the result is a necessary backbone of the working groups' monetary and knowledge influx. As also stated by the European Council (European Commission 4/24/2014), the modern communication of research via internet and the accessibility of information of all kinds, also of potential research of dual use, raises the question of necessity of information restriction. Yet, the freedom of publishing in online journals and the exchange of information and expertise is one of the modern developments that increase the possibilities of the benevolent researches (Deutsche Forschungsgesellschaft, Leopoldina 3/19/2010). This information can be used for a better understanding of life and improve scientific research processes, but also to harm and endanger "the health and safety of life on our planet" (European Commission 4/24/2014).

6.2 Responsibility of the researcher and call for supervision (Leopoldina)

Peter Strohschneider, president of the German research society, explained that science has consequences that lay outside the area of research e.g. new therapies, new technologies, new conditions and explanations of our world. These non scientific consequences are the problems underlying the dual use dilemma (DFG / Leopoldina 2014). He concludes that science itself and its results, namely the knowledge provided, are neutral to its consequences in first place and have no influence on them. The decision, how this knowledge is used, is made by other people than the researcher. He calls for rules and laws that are not neutral to those consequences and therefore are able to set dimensions that can determine them. We want to ask who is actually able to determine the potential risk and to weigh it against its potential benefits for society. Every scientific research can produce knowledge that can be used in a malevolent way. Peter Strohschneider names the risk of linguistics and psychology, but also informatics. As result of his conclusions, within the conflict of openness of science and the legal restrictions that might be necessary, one message becomes clear: The researcher himself is the one who makes the decisions, since up to now no legal restrictions apply. What is the potential danger of the work? Do the benefits outweigh the danger? Is there an ethical or moral reason not to investigate the question of concern? Which results can be published without concern? Which can be partly published? To answer these questions, Strohschneider argues, the Leopoldina and the DFG want to establish a new ethical institution for research composed of scientists from various areas of science. They help

initializing the ideas and guidelines provided by the commission of ethics and create a responsible and safe environment for research. In addition, as an important part of the consequent self-assessment and self-control proposed, freedom and responsibility of research and science is a dynamic topic that needs to be reassessed regularly (DFG / Leopoldina 2014).

6.3 Responsibility of the publishing institutions

Increasing communication technologies and the open source movement influence dramatically the ways research is published. To share ones' knowledge and results with everyone who is interested, one needs media, nowadays mostly journals that publish online, many of them free to access. The reviewers and editors of these journals make the final decision whether information is reaching the public. In many cases there "were calls for a complete ban of publication of such research or at least enforce censorship of manuscripts like pruning the methods section. The researchers and the editors were clearly unwilling to modify the manuscripts." (K. Satyanarayana 2011). In the case of the paper describing the reconstructed Spanish flu virus (Tumpey et al. 2005) which was handed in to *Science* and *Nature* at the same time, the NSABB was called for advice. They found the scientific benefits to outweigh the potential risk. "The editor in chief of the journal, however, subsequently wrote that he would have published the story even if the NSABB had voted otherwise" (Selgelid 2009). This clearly demonstrates the role of the NSABB as council, yet its recommendations impose no legal restrictions to researchers nor to publishing journals. The question of the necessity of a legal basis to decide on should be answered carefully, since several problems need to be considered. Who makes the final decision? Who is in the position to weigh the risks and benefits? Is it possible to foresee every risk that might occur? Are the people in charge able to make those decisions on ethical basis? Is self-governance of researchers and journals enough? Considering the broad range of research and possible fields of expertise, that might contain dual use risk: Is it even possible to create a law considering every misuse possible?

"To try to prevent misuse at the publication level serves little purpose, this is too late. By then, detailed knowledge about the contents of the publication is already known to collaborators, and the work has in most cases been presented at meetings. Through the long process of carrying out the work, it is most likely that detailed knowledge about the experiments has already spread to many persons and possibly even to online fora. The point of oversight and application of mitigating measures must begin at the planning stage and continue throughout the experimentation process until the work has been completed. This is why the risk assessment your Bielefeld-Team proposes is so important. Identify risks at the very beginning and find ways to mitigate those risks before any risk-laden methods become public knowledge."

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On the question of necessary measures to prevent dual use in interview with our team

Therefore, we propose a regular oversight as well as ethical guidance during the decision making. Further, assessment of dual use potential beginning with the education of researchers should be implemented. Nevertheless, in our opinion reviewers as well as editors need training about dual use issues and are part of the process of publication. Therefore, they are a necessary part of a responsible oversight process to prevent dual use.

6.4 Responsibility of the government vs self-governance

The NSABB, as the council for the US government, calls for institutional oversight of dual use research of concern. The need for openness to ensure progress in science and research as well as the need for oversight is stated. “Any oversight system must balance the need for security with the need for research progress. The degree of oversight should be consistent with the likelihood and possible consequences of misuse.” (National Science Advisory Board for Biosecurity 2007). So does the DFG and states that the need for security collides with the interest in publication of research results. This issue arises especially if the research is publicly funded, because the results are important for transparency, reproducibility, control and progress of research (Deutsche Forschungsgesellschaft, Leopoldina 3/19/2010). All participants are called upon to act responsibly to ensure the establishment of trust of the public in research and to minimize the risk of dual use. The researchers, funding institutions, cooperators and coworkers, reviewers, editors of journals, ethic councils and everybody involved are called upon to exercise responsibility. The need for risk assessment, documentation, communication, education and training is emphasized. The prohibition of proposed research has to be the last option of choice. The European Union calls for responsibility of all participants, too, but claims the need for an overseeing institution and underlying regulations (European Union 2014). All these acts of responsibility need to be carried out under national law and international law, yet there is no international agreement on dual use. Both NSABB (National Science Advisory Board for Biosecurity 2007) and European Union (European Commission 4/24/2014) set out for an international cooperation to ensure security in an international context.

The most popular case of governmental involvement in a dual use research of concern is the case of Ron Fouchier, Netherlands, who works on the Virus H5N1, published in *Science* (Ron A.M. Fouchier 2012). A Dutch court found the transmission of his paper to the headquarters of the journal a form of export and therefore that the national law on export of dual-use items applies (Rechtbank Noord-Holland, of 9/20/2013). The decision contradicts the assessment of the European Union Council that the transmission of knowledge is not necessarily equal to transport (European Commission 4/24/2014).

Another important aspect of governmental responsibility is the “establishing [of] mechanisms for advising on dual use research issues and assisting investigators in complying with dual use research policies. This should include the designation of a point of contact with the institutions for questions regarding dual use research” (European Commission 4/24/2014).

Although the Leopoldina, DFG and German ethic council proposed this as well (reference to the citation of professor Bora), we contacted the ethics commission of our university and found these mechanisms not to be existent yet. We asked about the purposes of the ethics commission at the University of

Bielefeld are. The initiative of the Leopoldina and DFG proposed the advisory of researchers dealing with dual use potential by an ethics commission. We interviewed the director of the commission, Gerd Bohner, concerning the experience of the commission with dual use issues and about the establishment of such an advisory committee. When he stated, that it had not been established yet, we asked about necessities for such an establishment.



“The ethics committee (EUB) reviews and evaluates planned studies, in response to researchers' applications, according to ethical criteria regarding the protection of human dignity, autonomy and self-determination of research participants; the evaluation results are reported back to applicants in a statement. The EUB provides help to researchers by giving advice on ethical and in some cases legal aspects of research with human participants. Independent of the EUB's evaluation, the responsibility for the research remains with the researchers themselves. The EUB does not fulfill the tasks of an ethics committee under public law according to the the law regulating health care professions [“Heilberufsgesetz”] of Northrhine-Westphalia [our

location] and does not evaluate planned research of a medical or pharmacological nature. One of our members might have more detailed knowledge about the dual-use question. I personally am aware of the existence of the joint committee of the Leopoldina and the DFG, which recommends the establishment of local committees for the ethics of research (KEF) at German universities. I know that Professor Bora from Bielefeld is a member of that joint committee. As explained, the EUB has different tasks than the planned KEF. The establishment of a KEF at Bielefeld University would require an initiative from the rectorate. My personal opinion is that the workload of a KEF might be larger than the one of the current EUB, and that its composition and work routines would certainly have to be organized differently.”

Prof. Gerd Bohner, Head of Ethics Commission, University of Bielefeld

6.5 Conclusions

Several proposals were committed from different, even international, institutions. They all call for the responsibility of each researcher and for the consideration of ethics and the underlying laws. Since the laws are not consistent and even the same law is applied and interpreted differently in different countries, the need for responsibility of the individual is as clear as the need for guidance by an ethic council. Since we are struggling to fully understand the broad range of ethical analysis and the applicability of international and national law to dual use questions and publication, one aspect becomes clear: Our team only consists of students of the life sciences. This is what we suppose most research groups to be like. We are no experts in ethics and law and we probably will not be, but we are able to cooperate in an interdisciplinary manner. This points out the necessity for the establishment of ethics committees as proposed by the Leopoldina/DFG. With a definite access to expert council and the establishment of awareness of dual use risk by educational processes, we all are able to act responsibly and plan our research carefully to minimize the risk of dual use.

7. Perspectives of biosecurity from the synthetic biology community

While many proposals and reports are written by advisors and professionals in ethics, politics and law, only a few reports are written by members of the synthetic biology community itself. Nevertheless, they are the ones producing the biological knowledge, as of now making the decisions about publication together with editors, which are often itself life science researchers. In addition, members of the community are the ones with each the best insights about the potential misuse of the knowledge they create in their individual research projects, since they are the only ones able to act at the very beginning of the research progress: the project design and planning. The community of researchers includes young researchers in education, such as iGEM teams, and non-professional researchers in so called garage laboratories and Do It Yourself (DIY) laboratories.

Jefferson et al. claim tacit knowledge to be of high importance for the enabling of researchers to work with commonly accessible knowledge. In addition, they identify five myths about synthetic biology that are commonly taken for granted, and discuss the relevance of those myths for the concerns of the public about the dual use potential of synthetic biology.

- „Myth 1: synthetic biology is de-skilling biology and making it easier for terrorists to exploit advances in the biosciences;
- Myth 2: synthetic biology has led to the growth of a DIY biology community, which could offer dual-use knowledge, tools, and equipment for bioterrorists seeking to do harm;
- Myth 3: DNA synthesis has become cheaper and can be out-sourced, and this will make it easier, for terrorists to create biological threat agents;
- Myth 4: synthetic biology could be used to design radically new pathogens;
- Myth 5: terrorists want to pursue biological weapons for high consequence, mass casualty attacks.“ (Jefferson et al. 2014)

In analysis of these myths, Jefferson et al. identify „important challenges to those myths“ (Jefferson et al. 2014). They find difficulties, that potential misusers would face if trying to design pathogens for bio-weapons. Not only the pathogen, but also the weapons need to be constructed, that is, the agents need to be ‘weaponized’. While the threat can’t be denied, it would not have the impact speculated commonly, because the conditions of synthesis of this pathogen would be imperfect without proper training, tacit knowledge and a specific skill set and laboratory. The authors suppose that „much of the debate in policy forums about the biosecurity threat of synthetic biology is based on naive and simplistic interpretations of synthetic biology’s ability to ‘make biology easier to engineer’ and in particular on the misleading assumption that the skills and knowledge necessary to perform synthetic biology will necessarily become accessible to people with no specialist expertise working outside professional scientific institutions, including hostile actors who would seek to misuse the technology to develop biological weapons.“ (Jefferson et al. 2014)

Another dual use aspect is discussed within the iGEM competition as well: the synthesis of drugs, namely opiates, by microorganisms engineered by synthetic biology. FBI Special Agent Edward You

presented the case of the synthesis of yeast strain producing opiates. Since it is used as a medical product, the study „could ultimately lead to cheaper, less addictive, safer and more-effective analgesics“ (Oye et al. 2015). On the other hand, opiates are misused as drugs and an easy to grow microorganism could provide an easier supply mechanism of the drug for illegal consumption as well. While the researchers „requested advice on how they might maximize the benefits of their research while mitigating the risks“ (Oye et al. 2015), they finally published their results and described all but one step. Another research group published that one step, making the pathway accessible for everyone. Oye and colleagues recommend four steps to avoid danger by these findings: the design of yeasts to „make them less appealing to criminals“, e.g. making cultivation harder, additional screening criteria for DNA synthesis including the opiate synthesis genes, physical security measures to prevent theft of the strain and regulations by law for this specific production way (Oye et al. 2015).

In addition, several iGEM teams have proposed the implementation of risk assessment and other tools to improve biosecurity assessment within the competition. We would like to introduce three of them. Team SDU-Denmark 2010 addressed the possible “malign use” with the proposal of questions for each team to ask itself. The questions can be found on their team’s safety page.

“Can host’s with this BioBrick survive storage conditions (in pressured conditions, under alternative temperatures and in large containers?)

Can your chosen host be aerosoled?

Does this BioBrick increase the host’s ability to vaporize?

Does this BioBrick increase the host’s ability to create spores?

Does this BioBrick produce any product that can regulate the immune system in animals or humans?

Is this BioBrick in anyway pathogenic in animals or humans or towards plants?
“(iGEM team SDU-Denmark 2010)

Additionally Team SDU-Denmark 2010 presented the idea of adding watermarks to a genome of genetically modified organisms and DNA parts. In case of release of the organisms into nature, sequencing could quickly reveal the origin of the organism or its DNA parts. This being a good implementation for biosecurity issues, it has not been realized yet and does not prevent the misuse of knowledge, but focusses on the organisms and biological parts itself.

Team KU Leuven 2013 stated the necessity for an integration of biosecurity issues and the awareness of potential misuse in education and found iGEM to be an ideal platform, as it is education young researchers. The team briefly explained the controversial needs for openness in science and the potential misuse of knowledge and protocols provided for the construction of weapons or other malevolent intentions. The call for responsibility of participants of the research progress, because “it would be unwise to let just one institution - be it the scientists themselves or one outside regulatory organ - carry the full responsibility” (iGEM Team KU Leuven 2013).

An oath was proposed by team Freiburg 2011, that included biosecurity aspects, such as “I recognize the power of synthetic biology and will apply it for the benefit of humankind”. In our opinion, this shows quite clear the responsibility of each member of the research process, not only in synthetic biology (iGEM team Freiburg 2010).

We acknowledge the work done by these and other teams, yet we find these proposals not to be sufficient to integrate the biosecurity risk assessment in iGEM. By implementing questions in safety forms and definitions in the safety page, the awareness of the biosecurity would be multiplied, because we believe not everyone to be aware of the safety projects of previous teams. Therefore, we propose risk assessment questions and definitions in chapter 8.

7.1 Conclusions

Hence, we find the authors to be pointing out one question about the relevance of legal restrictions for publication of such data. They ask for regulation concerning the release and distribution of opiate producing yeast strains. In our conclusion, every case of potential dual use will have to find the answer for the need for legal regulation if coming to term. To find a law applying to all potential dual use issues in research will be very challenging, if not impossible, without massive restriction of the freedom of science. Therefore, again, the need for responsibility of the individual researcher, everyone involved in the process and the possibility of professional council on ethics and law becomes clear.

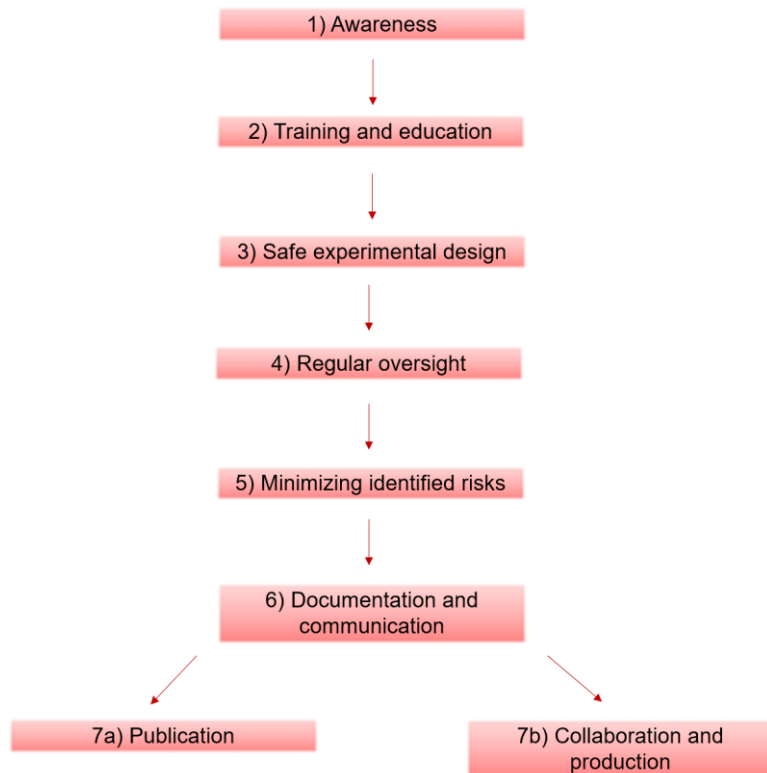
In addition, we find the need for biosecurity guidelines within iGEM to become clear. Several teams have already integrated biosecurity issues in their projects and policy and practice. Up to now, these issues have not been dealt with within the safety page and safety forms. We believe iGEM to have a great potential to increase the awareness of biosecurity and especially dual use risks, and the self-consciousness of each member by providing definitions and guidelines as well as expert counseling by the already existent team of the biosafety committee.

8. Proposed guidelines for minimizing risk of dual use

To guarantee the regular and responsible oversight of research, risk assessment needs to be done at all times. This includes not only the education of young researchers, but the oversight and responsible consideration of research by everyone involved. To grant this oversight, we propose actions basing on the proposals of the Leopoldina/DFG as well as the NSABB.

A) Underlying principles

While research provides advance and progress in several fields, it can create knowledge with the potential of being misused. Active participation in risk-assessment of researchers, publishers, federal agencies, funding institutions and the public, regular reassessment and regulated oversight of the potential of misuse can minimize the risk of current research to humanity and the environment. Public trust is essential for life sciences as they create information and technologies which improve many aspects of our daily life. To not only avoid danger, but create trust, open communication and risk assessment have a crucial role.



B) Prior to research activity

B.1) Awareness and risk assessment

“Awareness of the potential risk is a prerequisite for responsible research” (DFG / Leopoldina 2014). Hence, the knowledge of potential risks as well as its avoidance need to be assessed. Not only ones own action, but actions of potential collaborators, funding institutions and the public need to be considered. The potential for the misuse of the knowledge and possible products by third parties need to be taken into consideration. All participating parties need to be assessed for potential intentions and the protection against misuse. This assessment should be open and might make communication with overseeing agencies, ethic councils, supervisors, experts and possibly the public necessary. The actions to be taken need to be carefully considered, as no guideline can list every potential risk and the necessary steps to weigh them against their benefits.

B.2) Training and education

“In their university teaching and their training of junior scientists, researchers should communicate the principles of a responsible approach to research risks and set a good example. When doing so, researchers should also cover the subject-specific rules on risk minimization for their respective field of research. Researchers should also contribute to raising awareness about these issues when they carry out their project” (Deutsche Forschungsgesellschaft, Leopoldina 3/19/2010).

B.3) Safe experimental design

With awareness and education in safe project and experimental design, researchers are able to minimize risks by carefully planning their research. While the outcome of a project might differ from expectation,

the risk assessment needs to be carried on during the experiment and beyond. In addition, the researcher himself might not be fully aware of every possible risk. Oversight by third parties is therefore proposed.

B.4) Regular oversight

“Effective oversight will help maintain public trust in the life sciences research enterprise by demonstrating that the scientific community recognizes the implications of dual use research and is acting responsibly to protect public welfare and security. The federal agencies that fund life sciences research, the institutions that are the recipients of those public funds, and the individuals who conduct this research share this oversight responsibility” (National Science Advisory Board for Biosecurity 2007).

Implementing a regulated and recurring oversight of proposed work can help detecting and assessing dual use potential and minimize the risk. We propose a scheduled and organized system of responsibility for assessment of risk and regular reassessment not to establish control, but to increase the awareness of the relevance of the topic of possible dual use. The safety inspector’s tasks could be combined with biosecurity issues. This requires an education of these inspectors about the dual use issue and other biosecurity concerns as well as regular training and information about further responsible ethical and legal councils. He or she should be instructed to identify research as dual use concern, inform about the status of biosecurity and should be given instruments to establish structures to avoid risks and enable communication. These structures should follow an international agreement, such as the implementation of local, national and international councils and the establishment of procedures to follow if in any of the instances of dual use research of concern is detected.

“The foundation of oversight of dual use research includes investigator awareness, peer review, and local institutional responsibility. Such oversight allows input directly from the investigators, facilitates timely review, offers appropriate opportunities for public input, and demonstrates to the public that scientists are taking responsibility for their research.” (National Science Advisory Board for Biosecurity 2007).

C) Prior to and during research activity

C.1 Minimizing risks

Every person involved should take the necessary actions to minimize risks. That should take biosafety aspects following the law and institutional policies, but also biosecurity aspects into consideration. “This may result in the implementation of security measures (e.g. to prevent the release or theft of dangerous substances from laboratories) or special protection of the confidentiality of research results through physical, organizational and informational technology means (e.g. encryption of saved and transmitted data). Such security measures and access restrictions do not conflict with the requirement for transparency, because research results are not required to be made accessible for everyone at all times” (Deutsche Forschungsgesellschaft, Leopoldina 3/19/2010).

Possible collaborations, especially in an international context, need to be weighed carefully. Laws and requirements as well as the potential risk of shipping or sending biological agents, toxins or information

need to be considered. This is, especially of concern as the laws of the export of dual use goods might not only apply to goods, but also technology and knowledge.

Safety and security should be considered previous to, during and following the research activity.

C.2) Documentation and communication of risk

“If research entails risks for human dignity, life or well-being or for the environment or other significant values with constitutional protection, scientists should document these risks, how they weigh up against possible benefits, and the measures taken to minimize them both before and, in the event of changes, during their work. Scientists should bring this documentation to the attention of the research ethics committee responsible for these problems (...) or the head of their institution before the research begins.

Relevant risks and measures taken to minimize them should be noted on applications for research funding. Scientific advisory boards and other groups evaluating the research should be informed of these risks and measures as early as possible and should take a position on them in their reports” (Deutsche Forschungsgesellschaft, Leopoldina 3/19/2010).

D) Subsequent to research activity

D.1) Consideration of restriction of publication

As the sharing of knowledge is one of the vast improvements of our time and has provided progress to science, it should be considered of high value. In the context of dual use, the misuse and benefit of publication should be considered not only by the researcher, but by editors and reviewers of journals as well. For a profound decision process on this level, the responsible editors or reviewers should have access to training in both legal and ethical decision processes regarding dual use issues. The restriction of specific data without withholding information and inhibiting progress and collaboration should be considered. The delay of publication due to risk assessment by institutional oversight, federal agencies or ethic councils can be taken into consideration. While most journals and researchers aim for the quickest possible publication in interest of claiming intellectual property and being the first to publish on a certain topic, the oversight and delay might provide a security gain and should therefore be considered an option at least in very critical cases. The establishment of councils and oversight policies should grant a decision process as quick as possible. If a long delay is expected, this option is likely to be ruled out. Still the complete ban of publication is to be considered as the last measure.

D.2) Consideration of collaboration and production

Because research result are often meant to be sold to companies to create products or apply for patents, the cooperation partners and especially the potential use and misuse of a product or technology need to be carefully considered and discussed.

9. Can iGEM be a role model?

iGEM aims for an open source context within the field of synthetic biology. The ideas and results of every team are free to view for everyone. When establishing collaborations between teams from different countries, even continents, it is crucial to consider local regulations and laws regarding the use and shipping of devices, organisms or DNA fragments as well as the legal requirements of governmental oversight of the procedures and technologies developed and applied respectively. In many countries the dual use problem is recognized for chemicals and technologies that can be used for military purposes. The development and creation of genetically engineered microorganisms or potential pathogens that can harm the health of plants, animals and humans is widely considered a risk as well. The development of genetically engineered organisms as the purpose of the iGEM competition can provide knowledge for the synthesis of potential pathogens as well as the creation of dangerous chemicals as metabolites in the pathways of microorganisms and information about ways of manipulating the pathways. While this knowledge has the potential to be used in both benevolent and malevolent ways, the provision of this knowledge is widely not considered a threat and therefore not regulated by law in many countries. Consequently, we consider the knowledge provided on the teams' wikis as well as the providing of DNA fragments and devices to be potential research of dual use. We believe this is concerning, because the knowledge provided to create potential beneficial devices can be used to create harmful devices and pathways outside of the competition, as the provided knowledge is published under an open access agreement.

By acting responsibly and attentively in a field of international collaboration and information exchange of the generation of young researchers, in our opinion, iGEM participants have a unique chance of being part of a role model. Both responsible and free research by considering both benefit and risk of their projects can provide to a trustful interaction of public and researchers.

iGEM calls for responsible research and consideration of the benefit of the project of every team. The human practices ensure communication with the public and aim to build up trust in sciences by openness and discussion. Risk assessment is not only done by the participants, but overseen by regulatory institutions. Several forms and regular communications with experts in the headquarters aim to ensure biosafety and biosecurity implementations in every team. The question of dual use potential in the proposed research itself is addressed in the questions asked in project design:

„Who will use our product? “

„If your product is successful, who will receive benefits and who will be harmed?“ (iGEM Safety Page)

In addition, the FBI as federal agency is holding talks and informing and educating the young researchers in the topics of potential risk of research. Considering publication and possible collaborations, iGEM at present offers few possibilities to address any concerns, but calls for open communication if any issues are found during the project. Many processes for biosafety are established, such as safety forms and check-in of potentially harmful devices. The biosecurity and as a part of it, dual use, is not referred to. To further increase the awareness of the dual use issue, iGEM might strongly encourage every team to examine their project's dual use potential, e.g. as an additional part of the safety form. Within this, questions focusing on the potential increase of pathogenic mechanisms, creation of proteins with potential risk to environment or health, creation of substances with potential abuse as drugs and other harmful consequences could be asked. Each team could be required to do risk assessment of biosecurity

concerns, for example answering the questions in the US Oversight Policy, as we have done for our project in an additional document as an example. These questions do include some biosafety regulations already established in iGEM, but specify the concerns of experiments also with proteins or parts of these organisms. On advice from Prof. Nixdorff we propose a general biosecurity assessment. The biosecurity assessment cannot be separated from biosafety risk assessment strictly, because the biosecurity measures need to be appropriate to the biosafety risk. We propose to integrate questions into the safety form, in hindsight, that S3 toxins are banned in the iGEM competition anyway

Do you work with any sequences or toxins or plant/animal origin that might be a threat to health of humanity or environment?

Do you work with any S3 organism's sequences (or toxins) or does your work contain any sequences or proteins specifically produced/contained in these organisms? Do you provide any knowledge of constructing, manipulating or influencing these agents or toxins?

Do your experiments meet any of these criteria or provide knowledge about the conduction of these experiments?

- "Enhances the harmful consequences of the agent or toxin
- Disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification
- Confers to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies
- Increases the stability, transmissibility, or the ability to disseminate the agent or toxin
- Alters the host range or tropism of the agent or toxin
- Enhances the susceptibility of a host population to the agent or toxin
- Generates or reconstitutes an eradicated or extinct agent or toxin listed above" (United States Government)

Who has access to your laboratory?

Do the persons with access to your laboratory receive prior training?

Did you apply additional biosecurity measures to any substances? Describe the measures.

With an increased call for awareness and clear structure to avoid any potential dual use of the research performed and published, iGEM can be a role model. The infrastructure for the oversight is already established with the safety committee that includes professionals, which have been in contact with the dual use discussion. Necessary improvement could be achieved by enforcing awareness of the dual use matter in specific by asking for any dual use potential e.g. as additional part of the safety form. These additional questions could be as follows:

- Can you imagine any malevolent use of the knowledge and sequences published on your team's wiki? Could the knowledge you provide be used for the creation of products or organisms that pose a danger to humans or the environment?

- In case of collaborations, does the sharing of devices or information create the potential of misuse?
- In case of potential risk, did you initiate oversight or seek ethical/legal council or advice?
- How were your concerns addressed in your project?

“The iGEM competition can definitely be of educational character for young researchers and beneficial for trust building between public and research by showing responsibility that they are reflecting about not only biosafety but also biosecurity aspects of their work - that is, if the biosecurity issues are dealt with more consequentially than is the case up to now by requiring the teams to answer a biosecurity questionnaire that includes a dual-use biosecurity risk analysis as proposed by the Bielefeld CeBiTec-Team.”

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We would like to propose a short definition of the dual use dilemma and a very brief summary of actions for everyone involved in the iGEM competition. We aim to raise the awareness of dual use not only in the competition but for further careers of participants.

“The potential of knowledge and research results to be used in both benevolent and malevolent ways is referred to as dual use. It is an issue of biosecurity and needs to be considered in all stages of research, such as education of researchers, planning, conducting and publication of research. In national and especially international collaboration and publications, federal legislation and legislation of confederations like the European Union need to be taken into account. The careful weighing of the benefits against the risks, rather an ethical than legal question, is the responsibility of everyone involved.”

The definitions of biosafety and biosecurity could be integrated into the safety page of the iGEM headquarter. The very brief flowchart on the implementation of risk assessment could be displayed. In addition, participants could be called for awareness to make sure that potential funding institutions or collaboration partners will not use the information provided for different goals as originally intended. Furthermore, we propose an oversight of possible biosecurity issues and communication and discussion of the issue for awareness of security concerns. For example, teams could check each other’s proposed projects for possible misuse in addition to the questions in the safety form, as sometimes the assessment of one’s own project is not neutral. If there is concern about biosecurity or dual use, a further check by the iGEM headquarter, possibly the biosafety committees attending that have members with dual use experience, might be proposed. The oversight should nevertheless be of a non judgmental, advisory character, leaving the decision to the researchers themselves, as it will be the case in their future careers and therefore implement the educational character and purpose.



“The iGEM competition could strengthen responsible decisions on dual use research while respecting freedom of research if it provided the necessary resources. The competition offers already one resource by its very nature: iGEM is a good forum to discuss the issue. The second one needs to be developed: well-founded decisions about dual-use research need factual knowledge and normative considerations. Information about the facts and different normative perspectives on the problem could be published within iGEM and institutional points of contact might be

established. It would be great if such point of contact could provide counseling and help to examine the issue on all relevant aspects. The decision would still stay with the team and ultimately with every individual researcher. Therefore, any advice shall not get judgmental or take over the decision by giving specific recommendations.”

Constantin Teetzmann

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Taking into consideration the need for awareness of the dual use potential of research, especially in an open source context as is the iGEM competition, we propose to encourage our fellow iGEM participants now and in the future to address the potential misuse of their research in the competition and their further careers and not only consider the international regulations and national law, but participate in an ethical debate and establish processes as well as help establishing protocols in their local area to enhance biosecurity and awareness to ensure a responsible research and open communication for a trustful partnership between science and society.

Publication bibliography

Bureau of Industry and Security, U.S. Department of Commerce (2015): Policy Guidance, checked on 9/9/2015.

Cello, Jeronimo; Paul, Aniko V.; Wimmer, Eckard (2002): Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. In *Science (New York, N.Y.)* 297 (5583), pp. 1016–1018. DOI: 10.1126/science.1072266.

Daniel Patrone, David Resnik, Lisa Chin (2012): Biosecurity and the Review and Publication of Dual-Use Research of Concern. In *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science 2012, 2012* (Volume 10, Number 3), checked on 8/27/2015.

Deutsche Forschungsgesellschaft, Leopoldina (3/19/2010): Scientific Freedom and Scientific Responsibility. Recommendations for Handling Security-Relevant Research.

DFG / Leopoldina (Ed.) (2014): Freiheit und Verantwortung der Wissenschaft: Rechtfertigen die Erfolgchancen von Forschung ihre potentiellen Risiken? Symposium der Nationalen Akademie der

Wissenschaften Leopoldina, der Deutschen Forschungsgemeinschaft und des Deutschen Ethikrates. Halle (Saale), 03.11.2014.

European Commission (4/24/2014): Communication from the Commission to the Council and the European Parliament: The Review of export control policy: ensuring security and competitiveness in a changing world. COM(2014)244 final, revised Final.

European Union (2014): Commission Delegated Regulation (EU) No 1382/2014 of 22 October 2014 amending Council Regulation (EC) No 428/2009 setting up a Community regime for the control of exports, transfer, brokering and transit of dual-use items, checked on 8/22/2014.

Federal Foreign Office (Germany): Comment on Biological Weapons Convention (BWC), checked on 8/24/2015.

Federal Office for Economic Affairs and Export Control (Germany) (2015): Objectives of Export Control, checked on 9/9/2015.

Federal Republic of Germany (2012): Basic Law.

iGEM 2011: iGEM 2011 Security Page. Available online at <http://2011.igem.org/Security>, checked on 9/18/2015.

iGEM Safety Page: Safety Page, checked on 8/22/2015.

iGEM Team Lethbridge 2013: Policy and Practice, checked on 8/24/2015.

iGEM Team Peking 2010: Human Practice Home, checked on 8/23/2015.

iGEM team Freiburg 2010: Safety page. Answers to safety questions, checked on 9/9/2015.

iGEM Team KU Leuven 2013: Biosecurity, checked on 9/9/2015.

iGEM Team LA Biohackers 2014: Policy and Practice, checked on 8/28/2015.

iGEM team SDU-Denmark 2010: Safety Page. Questions for assessing parts, checked on 9/9/2015.

Jackson, R. J.; Ramsay, A. J.; Christensen, C. D.; Beaton, S.; Hall, D. F.; Ramshaw, I. A. (2001): Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. In *Journal of virology* 75 (3), pp. 1205–1210. DOI: 10.1128/JVI.75.3.1205-1210.2001.

Jefferson, Catherine; Lentzos, Filippa; Marris, Claire (2014): Synthetic biology and biosecurity: challenging the "myths". In *Frontiers in public health* 2, 8/21/2014, p. 115.

K. Satyanarayana (2011): Dual dual-use research of concern - öublish and perish? In *Indian Journal of Medical Research* 2011, Jan 2011. Available online at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3100136/>.

Leopoldina - National Academy of Sciences (2015): Mission Statement, checked on 9/9/2015.

National Research Council, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology (2004): *Biotechnology research in an age of terrorism: confronting the dual use dilemma*. Washington, D.C.: National Academies Press.

National Science Advisory Board for Biosecurity (2007): *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*. A report of the National Science Advisory Board for Biosecurity, June 2007.

National Science Advisory Board for Biosecurity (2015): Homepage - Description, checked on 9/9/2015.

Office of Research Administration - Institutional Biosafety Committee: IBC Applications, checked on 8/25/2015.

Oye, Kenneth; Bubela, Tania; Lawson, J.Chappel H. (2015): Regulate 'home-brew' opiates. In *Nature chemical biology* 11, 5/21/2015 (7), pp. 465–471.

Rechtbank Noord-Holland, of 9/20/2013, case number HAA 13/792.

Robert Roos (2014): Experiments render H7N1 virus more contagious in ferrets. In *CIDRAP News*, 4/4/2014.

Ron A.M. Fouchier (2012): Airborne Transmission of Influenza A/H5N1 Virus between ferrets. In *Science*, 6/22/2012. Available online at <http://www.sciencemag.org/content/336/6088/1534.full.pdf>.

Rosengard, Ariella M.; Liu, Yu; Nie, Zhiping; Jimenez, Robert (2002): Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. In *Proceedings of the National Academy of Sciences of the United States of America* 99 (13), pp. 8808–8813. DOI: 10.1073/pnas.112220499.

Russian Federation, United Kingdom of Great Britain, Northern Ireland and United States of America (3/26/1972): *Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction*.

Selgelid, Michael J. (2009): Governance of dual-use research. An ethical dilemma. In *Bull World Health Org* 87 (9), pp. 720–723. DOI: 10.2471/BLT.08.051383.

Terry Johnson: Traditional Biological Risk Assessment, checked on 8/23/2015.

Tumpey, Terrence M.; Basler, Christopher F.; Aguilar, Patricia V.; Zeng, Hui; Solórzano, Alicia; Swayne, David E. et al. (2005): Characterization of the reconstructed 1918 Spanish influenza pandemic virus. In *Science (New York, N.Y.)* 310 (5745), pp. 77–80. DOI: 10.1126/science.1119392.

U.S. Department of Health and Human Services (2015): NSABB - Frequently asked questions, checked on 9/2/2015.

U.S. Government (2015): Overview of U.S. Export Control System, checked on 9/2/2015.

United States Government: United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern. 14.06.2014, checked on 8/26/2015.

World Health Organization (09 2006): Biorisk management - Laboratory biosecurity guidance, 09 2006.

World Health Organization (2004): Laboratory biosafety manual. 3rd edition. Geneva, 2004.