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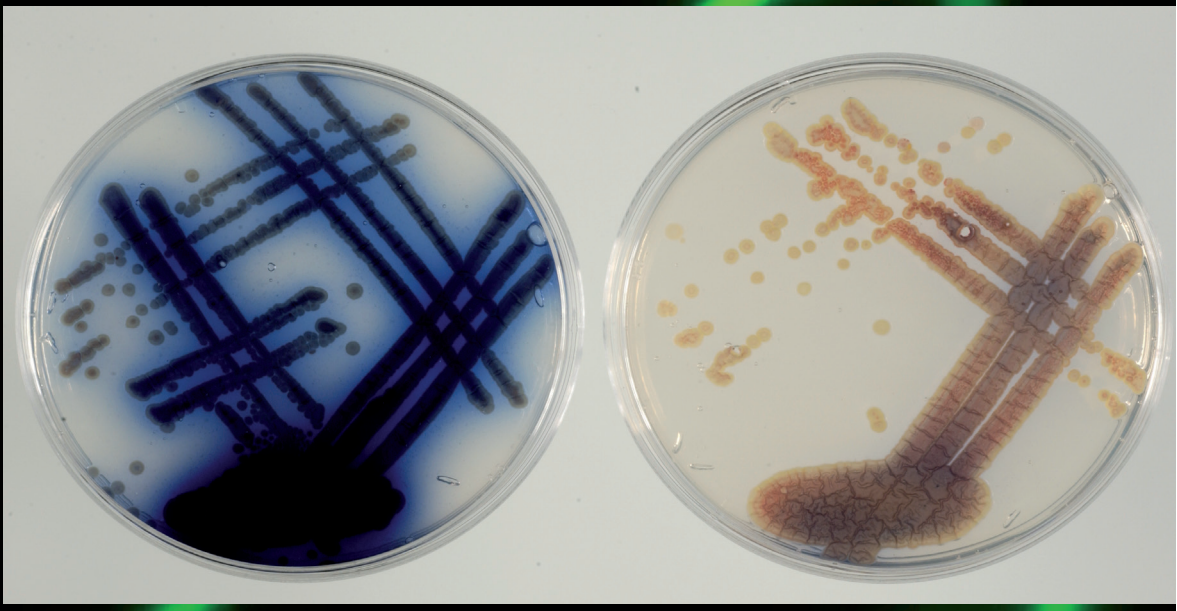
BIOSECURITY IN THE TRANSPORT AND TRANSFER OF BIOLOGICAL AGENTS



GOVERNMENT OF SPAIN
MINISTRY OF FOREIGN AFFAIRS AND COOPERATION
DIRECTORATE GENERAL OF FOREING POLICY AND SECURITY
SUB-DIRECTORATE GENERAL OF NON-PROLIFERATION AND DISARMAMENT

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Non-proliferation of biological agents

Background of cover and back cover: The genetically modified *Bacillus subtilis* bacterium over-producing a green fluorescent protein viewed under the fluorescence microscope.

Superimposed cover: The genetically modified *Streptomyces coelicolor* bacterium growing in solid medium and overproducing a blue pigmented antibiotic, compared with the nonproducer isogenic strain.

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INTRODUCTION

The International community adopted the "Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction" (BWC), held in London, Moscow and Washington on the 10th of April, 1972. Spain ratified the Convention on the 1st of June, 1979. The Convention aims to completely rule out the possibility of biological agents or toxins being used as weapons.

The United Nations Security Council (UNCS), concerned about the terrorism threat and the risk of non-state actors obtaining, developing or using nuclear, chemical and biological weapons, or trafficking with them, adopted the "Resolution 1540", on the 28th of April, 2004, which calls upon all States to take effective measures to prevent terrorists from using weapons of mass destruction (WMD), and the non-proliferation of those weapons by non-state actors; therefore, preventing biological terrorism. The UNSC Resolution 2325, on the 15th of December, 2016 resulted from the Global Review of the Resolution 1540 (2004) and emphasizes the non-proliferation of WMD by non-state actors.

Each State is responsible for the maintenance of its national security related to biological agents and materials. The main purpose of Biosecurity[1] is to strengthen the security concerning biological agents and materials, the facilities and activities related to them, as well as their

1 For the purpose of this document, Biosecurity is the physical protection inside and outside of the facilities containing biological agents, these agents, encompassing the associated equipment and materials, and their transport.

stockpile and transport; thus enabling a more effective fight against their illegal traffic, facilitating an appropriate preparation for an adequate response to a biological incident, either natural, accidental or intended.

Zoonotic virus outbreaks of avian influenza, Severe Acute Respiratory Syndrome (SARS), Middle East respiratory syndrome-related coronavirus (MERS), together with the recent epidemic of the virus of the Ebola in West Africa, have notoriously increased the concern about the potential use of biological agents as WMD.

The States Parties (SP) to the BWC did not agree to a verification regime for the biological weapons as yet. Thus, within the WMD, the biological weapons are the only ones who have not a Verification Regime. The absence of a BWC International Authority and a Verification Regime leaves biological weapons as the easiest to acquire by non-state actors or by States supporting terrorist organizations, thus facilitating its illegal traffic by criminal organizations.

These deficiencies in the international level increase the States' responsibility to design and establish measures at a national level to fulfil the UNSC Resolution 1540 (2004). The main issue for each State is how to organize itself manage to fulfil the obligations derived from the BWC and the UNSC Resolution 1540.

The Spanish Strategy for National Security comes as a Ministries Council's Decision on the 31st of May, 2013, features among its goals the designing and setting to work of a National Plan for Biosecurity, which, when officially approved, will provide a better fulfillment of the UNSC Resolutions 1540 and 2325. Biosecurity is, therefore, considered a matter of National Security.

Recommendations to improve Biosecurity measures are already published[2], setting in the goals of a national Biosecurity regime. The publication includes recommendations for the elaboration of a national strategy to deal with potentials biological attacks, and to keep the Biosecurity of materials and biological agents, in the handling of these agents as well as in the facilities whose personnel work with them and

2 Perez Mellado, Rafael. Recommendations for improving Buiosecurity measures. Madrid, Ministerio de Asuntos Exteriores y Cooperación. 2014.

in other related activities. This publication indicates the convenience of having a National Authority or Responsible Entity (RE) for the follow-up of the Biosecurity regime. A much recent publication[3] indicates how to model and improve biological measures in a simple and rational way.

Though in both publications it is mentioned the area of Biosecurity implementation, it exists the trend to think that the Biosecurity implementation remains limited to the facilities that work with pathogenic agents, excluding the concept of processes that are inherent to them, such as their transport, without excluding the transport and transfer (export) of those pathogens out of the jurisdiction and control of the exporting State, the convenience of designing codes of conduct for the personnel handling of pathogens in these processes and, to this end, the need of the pertinent security clearance issued by the Responsible Entity (RE) there described.

The most recent of the mentioned publications, reviews these measures, analyzing the logic of the given recommendations and simplifying the apparent difficulty of their implementations. The application of the common sense in this analysis, as in other areas of the WMDs, is a tool for proving efficiency.

The present document takes off from which has been already considered in that publication and, because of that, assumes the existence of an RE to monitor a national Biosecurity regime; it provides the clues to improve the application of Biosecurity measures on the transport of pathogenic agents, simplifying and supporting the control of their transfer to other countries and study the need of establishing a national Biosecurity culture.

The pursued goal is to minimize the possible sense of complexity and the wrong perception of the presumably high cost of maintenance of the given recommendations and the measures included. In other words, the establishment of a national Biosecurity regime is far from being out of reach and is reasonably manageable, both in its concept and in its implementation.

3 Perez Mellado, Rafael. Design and improvement of Biosecurity measures: a common sense exercise. Madrid, Ministerio de Asuntos Exteriores y Cooperación. 2016.

PATHOGEN TRANSPORT WITHIN THE NATIONAL TERRITORY

There are, at least, four different types of activities that involve the transport of pathogens within the national territory: *(a)* the transport of imported biological material from the country's entry point to the facility where this material will be delivered. *(b)* The transport between two facilities working with pathogens, both transfers of samples and/or pathogens. *(c)* Transport of samples taken at particular locations, as a result of an epidemiological surveillance process, to the facility where the samples would be analyzed or stored. *(d)* Transport from any point in the country to the final carrier that will transfer (export) the pathogen outside the national territory.

In all cases, the Biosecurity measures must be the same. Should the transport, carried out by individuals or by companies, both must have the appropriate clearance issued by the RE. It is crucial to avoid transport accidents which could result in the liberation of the pathogens in the environment; hence the transport must meet the corresponding Biosecurity requirements (type of vehicle, vessels, labelling, and maintenance of temperature required for each pathogen, etc.)

Biosecurity measures regarding security clearance must be the same for the transport of pathogens officially carried out by law enforcement agencies (LEA). If the transport is carried out by properly authorized companies, their personnel must have the appropriate clearance issued by the RE. During the transport, the company must keep a direct communication with the LEA, in order to ensure a rapid response if needed, covering possible accidents or unexpected incidents. The itinerary of the pathogens must be known and previously agreed by both, the LEA and the RE. Therefore, contingency and emergency plans must be approved by the LEA and the RE as an inherent part of the transport protocol.

To minimize the number of this type of transports, and the volume of samples potentially involved, it is advisable to keep this volume as small as possible (including the necessary duplicates or triplicates); so that transports containing a large number of samples will preferably

be those supplying samples to the reference laboratories in charge of stockpiling the samples (type culture collections) at the regional or national level. For instance, to minimize the volume of samples to transport, once the samples to be sent to the reference laboratories have been selected, the clinical analysis laboratories from hospitals should sterilize and destroy the rest of samples in situ to avoid unnecessary risks.

This philosophy could be applicable to other type of samples. For instance, should the regional or national collections be centralized, the number of deliveries would be minimized to and from public or private investigation facilities where those samples are needed, either for research or as reference material for that research.

In the absence of legislation concerning these situations and/or the operational mode in each case, the adoption of "Codes of Conduct" for the scientist and the facilities they are working in, could very effective, both in the public and in the private sectors. These Codes could be of a voluntary nature until they became compulsory if finally is so decided. The Codes would compile the basic norms of behavior and would help to minimize the risk in the facilities and in the transport of pathogenic agents and infected biological samples. The BWC working paper BWC/MSP/2014/WP.6 "Code of conduct for scientists" submitted by Chile, Colombia, Ecuador, El Salvador, Guatemala, Italy, Mexico and Spain, contains a model code of conduct which might apply.

TRANSFER CONTROL OF BIOLOGICAL AGENTS, BIOLOGICAL SAMPLES AND DUAL USE MATERIAL

Controlling the transfer of biological agents, biological samples and dual use material is of great importance to keep an effective surveillance on the pathogenic organisms and related material that get in and out the country, either by import or export processes, or by the simple transfer of biological samples between scientific or industrial facilities belonging to different countries. Protecting the country against a potential invasion by species of pathogenic organisms nonexistent in the country, is a critical measure of control which must be applied systematically, ruled by norms and supervised from the corresponding regulatory authority, either the RE or others, if the norms are to be supervised

from different governmental entities. In almost every country, there are import and export regulatory mechanisms which might broadly form the bases for a system to control the transfers of biological samples and agents.

1. Inventory of pathogens and biological related material

It is true that, for these control systems to be applied, a list of biological agents and related materials needs to be made. To make these lists, a good knowledge of the inventory of existing pathogens and related material in the country is required.

Pathogens will be doubtlessly found in four different types of facilities: *a)* clinical analysis laboratories from public and private hospitals and clinics; *b)* public and private University laboratories; *c)* laboratories from public and private Institutes and Research Centers; *d)* Research Laboratories and facilities designed to culture pathogens at large scale, both public and private. Gathering the corresponding information from all of them will need of two things: a document where all the information needed has to be provided by these facilities; and the appropriate legislation empowering the government to demand from different facilities the dully filled document.

The BWC working paper BWC/MSP/2014/MX/WP.6 "National application of the Biological Weapons Convention: A tool to evaluate facilities with biological agents", submitted by Chile, Colombia, Spain and Mexico, contains, in its annex, a "Questionnaire for the evaluation of facilities to carry out activities with biological agents requiring the use of containment laboratories", which might be useful to carry out the biological agents' inventory. The concept of containment facility encompasses all types of containment levels, from level one to work with the lowest risk organisms to level four to work with highest risk organisms. This questionnaire aims to evaluate the facility regarding biosafety and biosecurity measures in place, not only the type of biological agents manipulated in there, but their cultivation and stockpiled volumes.

2. Control lists

Regarding the control lists, pathogens naturally existing in the country are not the only ones to be considered, the list should also include pathogens which are not naturally present in the country, but could be of harm if imported, either by being more virulent or by the lack of appropriate prophylactic measures to fight them.

It is frequently considered that developing these lists becomes, administratively speaking, an extraordinary complicated task; yet, in fact, it might not be all that much. Usually, every country has epidemiological surveillance measures in place, which precisely enable the sampling and the transport of the collected samples to the facilities where they will be analyzed and/or store, etc. This existent regulatory norm does not probably need of a major update in order to make the lists and, also, supplies first-hand information for this purpose. The competence to gather the information asked in the above mentioned questionnaire is usually shared out among different ministerial units, such as Environment, Agriculture, Livestock, Human Health etc., but precisely all of them exemplify the existence of the norms that allow the gathering of the needed data in particular.

Pharmaceutical companies and other private entities which work with pathogens in magnitudes above the basic level in research laboratories, usually have the obligation to declare this and the agents used, either to the authorities entitled to give permission to work at an industrial level with these pathogens, or to the authorities entrusted to allow that level of production and its commercialization inside and outside the country (i.e. Ministry of Trade or Ministry of Industry). In other words, if the norms in place in the country were sufficient, it may not be necessary to draft new legislation, probably, compiling the data obtained applying the existing norms may turn to be enough. Alternatively, the RE could be in charge of applying these norms, or even better, supervise their correct functioning of them. Giving the RE this capability, once established, might not require the drafting of a complex legislation.

It is evident that not all the existing pathogens in the country have to be included in the lists, being necessary to set up selective criteria to

include the pathogens in these lists. An obvious criterion is to start the lists with pathogens known or strongly suspected to have been used as biological weapons or have been evaluated for their transformation in these types of weapons. Other criteria are usually added to this criterion such as the potential harm that some pathogens may cause if no vaccines or appropriate prophylactic measures exist. A paradigmatic case is the smallpox virus, which is known to have been used in the past as a weapon and, precisely because smallpox has been declared a worldwide eradicated disease by WHO, worldwide programs of preventive vaccination have been interrupted, therefore, the human world population is unarmed to the virus; the use of this virus by a terrorist would have disastrous consequences for the humankind. The smallpox virus is a candidate for heading any control list. Any other biological agent for which prophylaxis or effective vaccination does not exist and has highly incapacitating or lethal effects to human, animal or plant populations should form a part of the lists. The knowledge acquired in making the inventory of pathogens existing in the country should be of great help for the inclusion in the lists of those naturally existing agents or those routinely handled in the country that have the mentioned characteristics. Biological agents considered to be harmful which do not exist in the country, should also be integrated to the lists, as indicated above.

Not only the biological agents should be included in the lists, the biological related material should be also included, as long as it constitutes a source of concern as a possible transmitter or carrier of these biological agents, regardless whether these agents are specifically infective to humans, animals or plants. For instance, human or animal fluid samples could be contaminated by agents whose nature is unknown until the appropriate analyses are precisely carried out in the centers of reference to which the samples are being transported, either within the national territory or abroad, if they need to be sent to international reference laboratories. Samples containing tissues or theoretically inactivated organisms whose virulence are unknown that are shared among institutions for their evaluation in order to determine their possible efficiency as vaccine or for prophylactic assays in any of the different phases (one, two or three) required prior to their possible commercialization, could be also added to the lists.

The control lists should also include related dual use material, such as the equipment used to work with biological agents or equipment that not being designed with that purpose could directly be used or easily transformed to that end.

3. How to control the transfers

Administratively speaking, probably the easiest way to control transfers of the biological agents and related material included in the lists, might be mimicking the already existing mechanisms in the country to control the import and export of other materials, either generically or specifically (i.e. weapons). In fact, the number of export license applications related to biological agents that would eventually be granted would be very small compared to the volume of all types of goods, whether perishable or not, subjected to export controls.

Setting up export controls is often considered against existing bilateral or multilateral free trade treaties, or that it could damage that treading. Far from being the case. A free trade treaty is characterized by exempting or reducing customs duties on the export/import of certain goods, but all countries usually keep the right to control some goods or their components by several reasons, such as the protection of the national market, National Security purposes or environmental and/or sanitary safety. No free trade treaty should resent from including an export/import control of biological agents of national concern; moreover, the existence of this mechanism will not imply that the trading will not take place; it only means that an official authorization would be required for that trading to occur.

The use of norms already regulating goods transfers between countries has the advantage that the mechanism of this practice is already known and rarely requires additional legislation to be implemented; only the existence of one or a few additional lists of reference.

INTANGIBLE TRANSFER OF TECHNOLOGY AND THE CULTURE IN BIOSAFETY AND BIOSECURITY

The most difficult element to control, regarding the transfer of biological agents and related material, is the intangible transfer of tech-

nology (ITT). ITT refers to the technology, which being perfectly valid and of direct application to the improvement of the human, animal or plant health, might have components that may allow terrorists to use them to develop biological weapons or to directly use them to weaken the targeted population (human, animal or plant). There is not a way universally accepted, nor universally used to control this type of transfer. It is clear that the intangible technology is generated in all those facilities that work with pathogens, either public or private. The fact that companies pay a special attention to keep their technological progress from being acquired by their competitors makes them less likely to transfer their intangible technology. However, university laboratories and basic or applied research institutes, generically the Academy, that need to publish their findings in order to get financial support, making their research possible or the renewal of previously obtained grants to continue the started research, are obvious candidates to inadvertently transfer the technology.

Every country must try to find the way of minimizing the intangible transfer of technology. A possible way would be to create a Scientific Committee that determines, in the follow-up of the research projects financed by governmental contributions, the possible double use of the obtained findings, in order to exert a better surveillance and, eventually, to ensure that this research is not transferred in its entirety, so that its possible use with malicious purposes could not take place.

To be able to monitor and, eventually, to avoid this type of transfer, the culture in Biosafety and Biosecurity culture needs to increase in every country. This culture is only beginning to grow in some countries and it is simply non-existent in others. The level of the Biosafety culture could be estimated by the level of acceptance and adherence to the biological security regulations regarding the handling of biological agents (natural, genetically modified or generated by synthetic biology) by the users in their respective facilities; so that these regulations would have been assumed by them as inherent to the biological material they work with, narrowing down their questioning to how these regulations and their effectiveness could, eventually, be improved to the point of making no longer necessary to monitor their compliance. Regarding Biosecurity, as the cornerstone to avoid unusual outbreaks caused by

accident (e.g. inappropriate handling, inappropriate transport) or deliberate (pathogens acquired by criminal organizations or terrorists), the need of obtaining that culture is even stronger compared to Biosafety and it is further from being understood and assumed by the staff and the officials in charge of the facilities.

In an ideal world, the follow up on research projects, the evaluation of the possible double use that from this research could stem, the self-limitation in the publication of these results and the institutional or governmental compensation for this self-limitation, would likely be widely accepted and would configure the usual practice in the development of Science and Technology worldwide. In these conditions, the intangible transfer of technology would be practically non-existent. It is obvious that we stand still very far from this and that we have a long way to get there, but also it is very true that we have in our hands the capacity to shorten the time and to find out the way to succeed.