

Liberty to Decide on Dual Use Biomedical Research: An Acknowledged Necessity

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Abstract Humanity entered the twenty-first century with revolutionary achievements in biomedical research. At the same time multiple “dual-use” results have been published. The battle against infectious diseases is meeting new challenges, with newly emerging and re-emerging infections. Both natural disaster epidemics, such as SARS, avian influenza, haemorrhagic fevers, XDR and MDR tuberculosis and many others, and the possibility of intentional mis-use, such as letters containing anthrax spores in USA, 2001, have raised awareness of the real threats. Many great men, including Goethe, Spinoza, J.B. Shaw, Fr. Engels, J.F. Kennedy and others, have recognized that liberty is also a responsibility. That is why the liberty to decide now represents an acknowledged necessity: biomedical research should be supported, conducted and published with appropriate measures to prevent potential “dual use”. Biomedical scientists should work according to the ethical principles of their Code of Conduct, an analogue of Hippocrates Oath of doctors; and they should inform government, society and their juniors about the problem. National science consulting boards of experts should be created to prepare guidelines and control the problem at state level. An international board should develop minimum standards to be applicable by each country. Bio-preparedness is considered another key-measure.

Keywords Dual-use biomedical research · Liberty · Epidemics · Emerging infections · Bioterrorism · Biopreparedness · Code of conduct · Minimum Standards

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Introduction

When approaching the issue of liberty on dual-use biomedical research, it would be appropriate first to define “dual-use”. This term has been already used in politics and diplomacy to refer to technology which can be used for both peaceful and military aims. It also seems helpful to review how great men and thinkers perceive liberty.

Humanity entered the twenty-first century with considerable achievements in biology and medicine. A stormy development was noted in molecular biology and genetics, biotechnology, genomics, proteomics, nano-technology and signal replication. In health-care, synthesis of life-saving drugs, including hormones (e.g. insulin), development of vaccines, in vitro fertilization, gene manipulation in genetic disorders and insights in patho-physiology of diseases are among the most important achievements that improve the quality and duration of life. However, the shade of so called “dual-use” sometimes appears to creep up behind the scientific research [1–4].

In recent years the problem attracted the attention of scientific societies [5–8], research councils [9–11] and committees [12], stating the importance of preventive measures against bio-terrorism and creation of appropriate conditions for further development in biomedical research. Many authors provided historical overviews of the threat and its nowadays significance [13–15]. Scientists pointed on different aspects: the misbalance in funding [16]; the particular role of industry [17]; the need of a comprehensive analysis of the situation, and especially on defined criteria to recognize dual-use life-sciences research and assessment of balance between the threat and the possibilities for development in science [18–20].

Dual use biomedical research includes several categories of life-sciences research, where products, equipments or ideas might be malevolently used against people, animals and plants, against progress, and may cause illness, death, panic or disruption in social life. In some countries these items have been already regarded as a priority [7–10, 13].

The term “dual-use biomedical research” in this article will follow the accepted criteria of the National Science Advisory Board for Biosecurity (NSABB), USA [21–25].

Bio-medical research of dual use is research which may:

- enhance the virulence of microorganisms, causing diseases
- diminish the immunity of the host
- enhance the transmissibility of the pathogens (enhance the contagiousness)
- alter (enlarge) the host range of the pathogen
- render a vaccine ineffective
- confer resistance to life-saving antibiotics
- prevent diagnosis of infection or detection of a pathogen
- enable:
 - eventual weaponization
 - severity of disease/symptoms
 - mass casualty.

Great Men on Liberty

Going through the pages of “Thoughts and aphorisms” [26], the selection of Liberty funds [27] and the works of philosophers [28–31] (Table 1), I find, according to the opinion of famous philosophers, politicians, thinkers, writers and men working on culture and human progress, liberty is an understanding the needs of nature, responsibility and capability of action for better.

How can we translate liberty of choice while discussing dual-use biomedical research? What should we consider? Probably, we should take into account some recent events, the natural disaster epidemics, the emerging and re-emerging infections, the bio-terrorism and the future of bio-medical research. We should, of course, be guided by the most rational and ethical considerations: what would be the consequences of our action/inaction (the liberty to decide or not) for health, for life on the planet, for our children and for our achievements. In case of an action, how can we be prudent in decision favorable for further developments in life-sciences,

Table 1 Great men’s thoughts about liberty

Great men	Famous thoughts	References
Writers, musicians		
Goethe	Liberty is the capability of doing what is reasonable under all possible conditions	[26]
Charles Gounod	Liberty is a conscious and voluntary obedience to the eternal truths	[26]
George Bernard Shaw	Liberty means responsibility	[26]
Heinrich Heine	Liberty is a symbol of new religion, the religion of modernity	[26]
Albert Camus	Freedom is nothing else but a chance to be better	[27]
Politicians		
Thomas Jefferson	The price of freedom is eternal vigilance	[27]
John F. Kennedy	(a) We shall pay any price, bear any burden, meet any hardship, support any friend, oppose any foe, in order to assure the survival and the success of liberty (b) Liberty without learning is always in peril; learning without liberty is always in vain	[27] [27]
Philosophers		
Montaigne	The true liberty is to be able to do what a man will with himself	[28]
Spinoza	(a) Liberty is to know the needs of nature, free is the one who is following reason (b) ... that state is the freest whose laws are founded on sound reason, so that every member of it may, if he will, be free, that is, live with full consent under the entire guidance of reason	[26] [29]
Kant	... the idea Freedom, common to both these, render necessary a distinction of duties into the offices of outward and those of inward liberty, whereof the later one is moral	[30]
Plato	Each time there is full liberty of choice	[31]

but which at the same time should guarantee national security (as liberty is a responsibility).

Some Recent Events—Shades from the Past

Let me remind you some recent events.

The world was shaken by the terrorist attacks on the USA on September 11, 2001, and during October, 2001 when anthrax spores were disseminated in letters in the USA. The terrorist attacks in Spain, the UK, Turkey, Japan and elsewhere in the world have shown clearly the face of a real threat.

Recently, important scientific results, such as the sequenced genomes of particularly pathogenic agents, the “Spanish” influenza virus that caused the pandemic in 1918, the poliomyelitis virus and *Bacillus anthracis* [32, 33], have been published without taking account the possibility of a potential mis-use. Similarly, gene manipulations on *monkeypox* virus, resulting in disruption of immunity in the infected mice, were reported without preventive measures [34]. *Polio* viruses have been synthesized in the laboratory (which is a great scientific success) and the results were again reported without precautions [35–37].

However, we should point out, because of internationally available virus sequencing data and co-operation, the SARS-CoV was identified in 2002 and the epidemic was contained [38].

It should be emphasized that bioterrorism and dual-use life-sciences research are not recent events. Since antiquity severe infectious diseases have been used during wars against the enemy [39, 40]. At the beginning of twentieth century bio-weapon programs were developed [41, 42].

Natural disaster epidemics have depopulated the world several times [14, 43–45]. Most of diseases are zoonoses¹ and have not been eradicated [46–50]. Smallpox has been eradicated, but could be mis-used for bio-terrorism [14, 45].

Natural Disaster Epidemics and Potential Bioterrorism Agents

When discussing several severe pandemic² infectious diseases, we should emphasise that there is a possibility that they could also be used intentionally (as bio-weapons).

According to contemporary knowledge and data analysis, experts consider that bio-weapons will be used as priority weapons for mass casualty, because they are not-expensive, may be easily obtained, could be difficult for recognition and identification, have a huge potential for morbidity, lethality, epidemic dissemination and to cause panic, disruption in society and economic losses [14, 39–42]. Laboratory accidents can also represent a significant danger both for the laboratory staff and the society [3, 4, 14].

¹ Infection primary in animals, people may attract infection from infected animals and their products.

² A huge epidemic that spreads through countries and continents.

Table 2 Selected examples of natural disaster epidemics that may be used intentionally as bio-weapons

Disease and pathogen; Main references	Mode of transmission (MT), Incubation period (IP) ^a First symptoms (FS)	Typical symptoms (TS), Lethality (L)	Antibiotic therapy (AT), Specific prophylaxis (SP), Infection control (IC)	Facts and comments regarding bio-weapon potential
Smallpox— <i>Variolla virus</i> [45, 51–54]	MT: respiratory ^b and contact IP: 7–21 days FS: high fever, discomfort, headache, pain in muscles	TS: rash, starting with vesicles on the head, face, chest and extremities, all eruptions are at the same stage, a typical fever curve L: 20–50% in Variolla major	AT: Acyclovir SP: vaccine—emergency vaccination (up to the 4th day post-exposure to patients + contact people IC: respiratory ^b (respirator ≥ N95) + contact isolation	Variolla has been used in past military conflicts During 1st and 2nd world war and “cold” war experiments and stockpiles took place People are not vaccinated Clinical diagnosis takes time— contact people would have attracted disease Disease has been used in past military conflicts
Plague, “black death” – <i>Yersinia pestis</i> [43, 49–54]	Zoonosis ^c , MT: in nature, mainly by the fleats of rodents, resulting in bubonic form; other more severe forms are plague pneumonia, MT: respiratory ^a , with high transmission person to person; and septic plague IP: 1–4 days	TS: (pulmonary form)—severe febrile disease with fever, cough, blood in sputum, difficulty in breathing quickly progressing to respiratory death L: close to 100% within 1–2 days	AT: ciprofloxacin, if used very early SP: not available	During 1st and 2nd world war and “cold” war experiments and stockpiles took place Effective aerosol dissemination has been documented, e.g.—high potential

Table 2 continued

Disease and pathogen; Main references	Mode of transmission (MT), Incubation period (IP) ^a First symptoms (FS)	Typical symptoms (TS), Lethality (L)	Antibiotic therapy (AT), Specific prophylaxis (SP), Infection control (IC)	Facts and comments regarding bio-weapon potential
Anthrax— <i>Bacillus anthracis</i> [14, 44, 51–53]	Zoonosis ^c , MT: in nature— contact, alimentary, rarely respiratory ^b , but inhalational anthrax is more severe IP: 1–6–60 days	TS—(pulmonary form)—abrupt temperature rise, chest pain, nausea, vomiting, cyanosis, sweating, dyspnea, shock; widen mediastinum is a typical X-ray finding L: 85–90%	AT: ciprofloxacin SP: vaccine IC: respiratory ^b (particle respirator \geq N95) and contact; decontamination is important	Experience is based on an incident in Sverdlovsk, 1999 (69 people died), and 2001 terrorist attack in the USA with anthrax spores contaminated letters (5 people died) Spores are extremely resistant— appropriate for aerosolizing powder

^a The time between the exposure and appearance of first symptoms

^b A transmission through respiratory secretions: a droplet transmission includes particles >5 micrometers and requires close contact with the infected person; the air-borne includes the dried infectious nuclei of respiratory secretions <5 micrometers, which may stay in air, contaminate surfaces and be present in the dust away from the patient

^c Infection primary in animals, people may attract infection from infected animals and their products

CDC, Atlanta, recognizes several categories of select agents (viruses, bacteria, fungi, toxins, genetic elements, recombinant nucleic acids, and recombinant organisms) published in alphabetic range in the last edition [51].

Let us focus on several natural disaster pandemics caused by pathogens which may be used as bio-weapons (Table 2). It is considered that the pathogen, when weaponized, may be preferably transmitted via an air-born mechanism. The consequences would be more deadly disease and symptoms that are difficult to associate with a particular disease.

Emerging Threats

Which are the most threatening emerging and re-emerging infections? Some of them are presented in Table 3.

List of viral, bacterial, fungal and parasitic emerging and re-emerging infections is long. We should point out in brief the pulmonary tuberculosis. Tuberculosis, an old disease, considered almost eradicated in developed countries, is re-emerging now with severe variants—multidrug- and extensively-drug resistant tuberculosis (MDR-TB and XDR-TB). Pulmonary tuberculosis is typical example of air-born infection and *Mycobacterium tuberculosis* spreads person to person via nuclei of respiratory tract secretions containing microbes. MDR strains are defined by resistance to isoniazide + rifampicin (two basic anti-tuberculosis drugs), while the XDR-strains are additionally resistant to at least one fluoroquinolon and one second line parenteral drug [64]. The treatment is very difficult, longer and more expensive than treatment of infections with susceptible strains. The resurgence of tuberculosis and the presentation of MDR-TB and XDR-TB is generally associated with non-compliance with treatment, as well as an infection in HIV-infected patients or poverty. There is a BCG vaccine and other vaccines under development. Infection control necessitates air-born isolation with respiratory masks and respirators; and protection of laboratory workers by use of safety cabinets. Aerosol dispersion of MDR- or XDR-TB strains as bioterrorist attack may have significant health-care consequences.

Diagnosis of the Emergency Event

Recognition and clinical diagnosis of first cases by general practitioners, infectious diseases-specialists, emergency department staff and other health-care workers will be critical. Rapid diagnosis is of vital importance for the successful treatment and control of infection. The diagnosis might be difficult, because of unusual illness, typically not considered, the symptoms may differ from the natural appearance because of atypical spread, and the disease might not have been seen in this region previously [51–54]. In such situations, several patients with similar symptoms should be considered an outbreak. It is necessary to emphasize that to be successful, the emergency post-exposure prophylaxis and treatment with vaccines and antibiotics respectively, if available, should start immediately since the exposure.

Table 3 Selected examples of emerging diseases, that may be used intentionally as bio-weapons

Disease and pathogens; Main references	Mode of transmission (MT), Incubation period ^a (IP), First Symptoms (FS)	Typical symptoms (TS), Lethality (L)	Antibiotic therapy (AT), Specific prophylaxis (SP), Infection Control	Data and comments regarding eventual intentional use
Viral hemorrhagic fevers: Ebola HF, Marburg HF (<i>Filoviridae</i>); Lassa HF (<i>Arenaviridae</i>); Crimean- Congo HF (<i>Bunyaviridae</i>) etc. [51–56]	MT: from infected animals or arthropod vectors; person to person: contact with blood and body fluids; air-born or post-mortem IP: 2–21 days FS: fever, malaise, pain in muscles, joints; ± diarrhea, nausea, vomiting; ~ 1 week	TS: Rash, conjunctival injection, periorbital oedema, prostration, pain in: throat, chest, abdomen; bleeding and shock L: high	AT: not available SP: not available. IC: contact and droplet (air-born) precautions—particular respirator ≥ N95, with eye protection: face shield/goggles; safe injection practice; safe burials	Diseases are geographically located (conditions for the mosquitoes, ticks and animal reservoirs). For bio- terrorist goals both viruses, infected animals (baths, monkeys, rodents) and infected vectors may be used, especially viral/ mosquitoes aerosols
Severe Acute Respiratory Syndrome (SARS- associated <i>Corona virus</i> (CoV)) [54, 57–59]	MT: air-born; disease appeared in 2002 in China and spread to Singapore, Korea, Vietnam, and Canada IP: 2–10 days FS: flu-like	TS: Cough and severe respiratory symptoms (pneumonia), followed by inability to breathe L: 10%	AT: not available SP: not available IC: isolation room, mask over the patient's nose, mouth; for medical personnel: respirator ≥ N95	Intentional use of SARS-CoV through inhalation may give the beginning of world pandemic
Avian influenza: <i>virus</i> H5N1 [54, 60]	MT: the strain with higher contagious and lethality potential for humans is carried and transmitted by birds (saliva, nose, feces)	TS: Severe pneumonia	AT: oseltamivir SP: not available IC: same as in SARS + veterinary control	Disease could be used intentionally to cause human and poultry/ economic losses, using viral aerosols, infected birds and poultry products

Table 3 continued

Disease and pathogens; Main references	Mode of transmission (MT), Incubation period ^a (IP), First Symptoms (FS)	Typical symptoms (TS), Lethality (L)	Antibiotic therapy (AT), Specific prophylaxis (SP), Infection Control	Data and comments regarding eventual intentional use
Transmissible spongiform encephalopathies (TSEs)— Prions ^b [61]	MT: for Creutzfeldt-Jacob disease (CJD) sporadic/ familial, nosocomial/variant (v)—through infected animal products; IP: long	TS: Neurological changes and dementia; L: within 2 years in CJD; CJDv—longer duration, neuro-psychiatric symptoms early	AT: not applicable SP: not available IC: veterinary control; in hospital care special regimens of sterilization are required	Infected animals, their products, contaminated equipment may contribute to someone's improper goals
<i>Nipah</i> and <i>Hendra</i> —viruses (<i>Paramyxoviridae</i>) caused infections [51, 62, 63]	Both viruses share a common reservoir—baths; MT: close (respiratory ^c) contact with infected animals (pigs/horses respectively)	TS: Both viruses cause severe encephalitis	AT: ribavirin (in vitro—OK)	Although there is a geographic distribution, an epidemic may be started by using viruses or intermediate animals/their products
			SP: not available IC: recognition of infection in swine/ horse is crucial	

^a The time between the exposure and appearance of first symptoms

^b Conformationally changed protein with a potential for accumulation and transmission

^c A transmission through respiratory secretions: a droplet transmission includes particles >5 micrometers and requires close contact with the infected person; the air-borne includes the dried infectious nuclei of respiratory secretions <5 micrometers, which may stay in air, contaminate surfaces and be present in the dust away from the patient

In this respect the rapid (real-time microbiological diagnosis/identification of the pathogen is crucial (the development of typical clinical symptoms usually requires more time).

What Measures Should We Take to Decrease the Dual-Use Potential in Bio-Medical Research?

In the light of the thinkers' and philosophers' legacy, and having taken into account some recent events—the natural disaster epidemics, the emerging and re-emerging diseases, the potential for bio-terror events we already have—I consider our categorical position is that there is not time to wait and we should decide on dual-use biomedical research. Today, in 2008, the following issues seem reasonable:

First of all, the Scientific Community, the scientists creating the progress in biology and medicine, should be aware of the dual-use dilemma [65]. They should be educated to be careful and know how to keep their own developments away from a potential mis-use. Secondly, it is considered that *The Code of Conduct of Scientists* will play a central role in future scientific work [66]. The Code of Conduct of scientists, criminalizing bioterrorism and mis-use of dual-use bio-medical research, should be regarded as a Scientists Oath in front of the society, as an analogue of the Hippocratic Oath of doctors [67].

When thinking what should we do, in the context of the views of the acknowledged scholars and experienced men, e.g. “to assure the survival and success of liberty”, we should be aware of potential dual use at every stage of research, when planning, acquiring grants, conducting, and publishing it. It also seems a priority to perform research that would enable us to overcome the emerging and re-emerging diseases, the natural zoonoses and other diseases that may be used as bio-weapons. To answer the question “How can we prudently continue biomedical research?”, we say by introducing security measures. When the desire is for scientific research to progress with security, the next question is “At what price?”. Scientific decision should be very precise and competent [68].

An important step in the total organization of the defense against dual use will be the creation of a National Reference body (from scientific and security experts and other relevant specialists, on the model of the National Science Advisory Board for Biosecurity, USA). The Board should be charged with elaborating the National Guidelines, to precisely define the criteria and risks, to consult Government on the issues related to dual-use bio-medical research, as well as to have reference and control functions. Appropriate legislation is also required, and it may be that this should precede the other measures [13, 66].

We should not forget to inform and educate society appropriately. The sense is that these measures are undertaken to protect society, and to be successfully introduced and conducted they need to be well understood and accepted.

It is more than clear, that the dual-use dilemma is not only a national, but rather an international issue [4, 69]. In this regard, establishing an International Committee seems more than necessary. Its tasks would be:

- to elaborate the Minimum Standards to be applied by every country
- to co-ordinate the world scientific society efforts to conduct research in atmosphere of openness, trust, to support organizing and implementation of multilateral projects, mutual exchange of data, information, ideas, experience, opportunity to work with the best specialists and at leading world centers
- to guide/help individual countries in organizing conditions for secure measures when performing dual-use biomedical research
- to serve as higher reference organism for consultations and specialized advices
- to co-ordinate relations with appropriate international organizations, such as WHO, the UN, the EU, NATO and civil organizations, working on biosecurity
- to create a network of reference laboratories for surveillance of the epidemiological situation
- to develop plans and resources for emergency aid.

Recommendations Concerning the Minimum Standards

The Minimum Standards should be designed not to limit bio-medical research and bio-medical researchers, but to ensure secure measures to protect them.

The Standards should approve the Code of Conduct of scientists and put it in action; they should support introduction of appropriate security measures at each stage of biomedical research, and for particular type of facility/institution, starting with laboratories performing work at biosecurity level 4 (dealing with the most contagious agents, without reliable specific prophylaxis and therapy) and through academic, university-, hospital-, industry, governmental and private-, civil and military-facilities. In this regard, the institutional scientific/ethics committees should be given more rights and powers to perform responsible evaluation of projects (as well as of new personnel).

The Minimum Standards should consist of most important rules and guidelines for their implementation; they may be specialized upon human/animal/plant-pathogens/diseases—from one hand, and advanced DNA- and other technologies, from the other, and could be accepted as official legislation. Preliminary negotiations with official countries agencies, scientific organizations and individual scientists may be necessary steps in rising awareness, promoting discussions and compliance.

The secure measures aim to protect both life-sciences research and society against malevolent use of scientific ideas, methods, products, equipments, tests, materials. Appropriate basis, when preparing the Minimum Standards, will be the criteria and other guidelines of NSABB for “dual-use” life-sciences research and the List of “Select agents” of CDC, Atlanta. The programs by WHO and other organizations to contain emerging and re-emerging diseases provide experience in reference laboratories and centers which may be further developed and included in a global network of surveillance.

Such type of epidemiologic surveillance is required for the bio-preparedness as a key-bio-defense [14, 69–73]. Preparedness to meet the emerging and re-emerging infections, the natural disaster epidemics, or bio-terrorist attacks requires similar

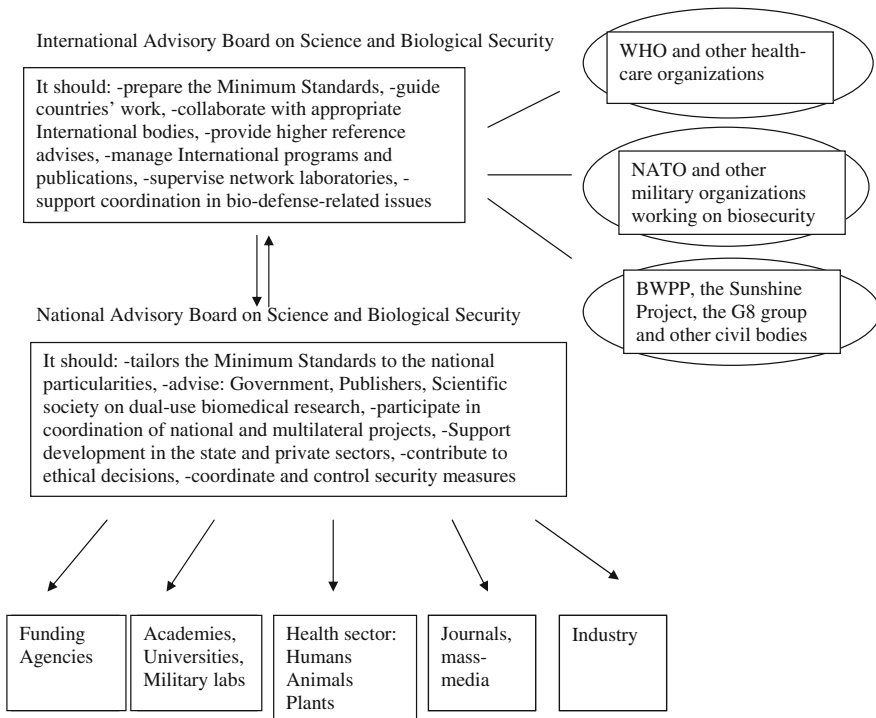


Fig. 1 Proposed scheme for organization of secure measures in dual-use biomedical research. *Legend:* WHO, the World Health Organization; NATO, the North Atlantic Treaty Organization; BWPP, the Bio-Weapons Prevention Project

organization, complex plans, coordination, adequate infrastructure and financial resources. In the health-care sectors we should consider appropriately equipping hospitals/departments, including intensive care units, microbiology laboratories with possibilities for real-time diagnosis, well educated and appropriately trained personnel, facilities for isolation, quarantine, stocks of drugs and vaccines. Personal protective equipments should be provided for the medical personnel, for people working at front line in the field, such as policemen, firemen and for all people that will take care of the patients etc.

Recommendations Concerning Advisory Committees on Science and Biological Security

Both the National Advisory Committee/Board on Science and Bio-security- and the International one- should be multidisciplinary. As it has been already discussed in the beginning, the bio-medical sciences are under extreme development, they become more and more complex and multi-faced: new sub-disciplines appear. The Boards should include experts in both life-sciences (microbiology, virology, infectious diseases, molecular genetics, immunology, bio-technology, bio-signal regulations, nano-technology, veterinary medicine, agriculture, food and water

specialists) and in security, defense/military, legislation, internal and external affair officers, a specialist in risks assessment and prognosis, a psychologist, coordinator from government, representatives from foundations and trusts supporting research, journals' publishers and editors. It would be appropriate the Boards to have lists of consultants to assist them when a particular question in a more-narrow field arises. The Boards should operate quickly and the experts should be in touch. The International Board will have a variety of coordinating functions—with countries with different national and political organization, different culture and particular structure of responsible agencies and different economic development. On the other hand, it would maintain relations with many international organizations, societies and groups—with different profile:—health-care, scientific professional, civil, military, humanitarian, and religious and other kinds of organizations. In this regard it is important that the committee members act not only defending the national interest, but also in favor of common welfare and respect of the principles of ethics and liberty. Organization of such type would be able to cope with some difficulties, already noted in the recent review by Bonin [74].

Figure 1 summarizes the recommended scheme for organizing secure measures in “dual-use” biomedical research.

In Conclusion, if we take into account the natural disaster epidemics, the emerging and re-emerging diseases, the huge potential of organisms that may be mis-used as bio-weapons (or may be involved in a laboratory accident), we will see, that the liberty to decide on dual use biomedical research is an acknowledged necessity. In this respect we should continue research implementing preventive measures and develop bio-preparedness at national and international levels. We should create National and International Advisory Boards on Science and Bio-security, to develop the Minimum Standards aimed at secure development in biomedical research, and give priority to working international projects and programs.

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