REVIEW ARTICLE

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The concept of operationalization of an integrated platform for scientific research and expertise of war and bioterrorism biological agents

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Abstract: *The international situation requires a strengthening of the national security measures, including in the field of CBRN and public health. The upgraded microbiology laboratories from DM/ MND must be operated at full capacity for the operationalization of an integrated Platform for the research and expertise of biological war and bioterrorism agents. This is necessary for reasons of national security, for CBRN defense and for public health, in the context of biological agents of 3 and 4 risk groups' epidemics.*

The existing upgraded objectives should be operationalized in order to meet the established scope: scientific research and expertise of biological agents and biological weapons, a laboratory for in vitro analysis and a bio-base for in vivo analysis. The highly secure lab allows working with any high-risk agents: biological, genetic, chemical, radiological, etc., being provided with a special room for the insertion/removal of equipment and their decontamination.

Following an increase in the capability requirements concerning laboratories, we have provided in the design concept new technical parameters of the platform and the integration of new compartments with related activities of toxicology, pathology, neuro-psycho-pharmacology, bio-pharmacy, micro-pharmaceutical, specific testing activities, etc.

Creating the integrated platform and its operationalization is necessary in order to meet the requirement of the national security strategy as a collective CBRN defense/protection facility and military-medical scientific research for CBRN medical protection.

Keywords: *biological agents, bioterrorism, medical protection, microbiology laboratory, scientific research, integrated platform, CBRN*

INTRODUCTION

The international situation requires a strengthening of the national security measures, including in the field of CBRN defense (chemical, biological, radiological and nuclear) and public health. The upgraded microbiology laboratories from the Medical Department of the Ministry of National Defense (MD/MND) must be operated at full capacity, for the operationalization of an integrated Platform for the scientific research and expertise of biological war and bioterrorism agents. The project is necessary for national security purposes, for CBRN defense and for the public

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health, in the context of biological agents of 3 and 4 risk groups epidemics, and it responds to current threats. In risk group 3, are listed extremely dangerous bacteria and other pathogens such as warfare biological agents (WBA). In the maximmum risk group 4, are included 8 species of extremely dangerous viruses such as Ebola or WBA viruses.[1,2,3]

Current regulations take into account the provisions of biosafety (such as internal protection for operators), of biosecurity (as protection against facility external hazards) and of bioprotection (protection of the sample to be analyzed). As a result, laboratories are properly classified, depending on the different level of protection. In French literature they are referred to as P1-4 (Protection).

The key features are: P1 with open work areas for education; P2 with biosafety hoods, for medical purposes; P3 special biosafety equipment for the extremely dangerous bacteria; P4 for the extremely dangerous viruses, with the maximum level of biosafety. In English, they are called Biosafety Laboratory (BSL1-4).[4] In Romanian, they appear as Basic Labs with a level 1 and 2 of biosafety, Highly Secured Laboratory with a level 3 of biosafety, and a highly secure laboratory with a level 4a of biosafety (with collective protection equipment) and 4b (with special equipment for individual protection). In the absence of proper facilities, the biological agents classified in the risk categories cannot be legally worked with. [2]

STATE-OF-THE-ART

Nationally, the Ministry of Health has modernized a microbiology lab at the National Research Institute “Cantacuzino” as a P3 laboratory and one (under construction) at the Bucharest Hospital for Infectious Diseases "Babeș". The Ministry of Agriculture has two P3 microbiology laboratories at the Bucharest Institute for Animal Diagnosis and Health. Currently, in Romania, a P4 highly secure microbiology laboratory does not exist yet.

Due to the fact that in Romania scientific research for medical protection against CBRN agents belongs to MND, it is mandatory to have a proper facility. According to Biosafety in medical laboratories Guidelines (World Health Organization 2004 and Ministry of Health 2006) the bacterial biological agents are expertised in the P3 laboratory, and the viral agents in a P4 laboratory.

The international context shows that eventhough the risk of biological warfare has decreased as a result of the Geneva Convention (BTWC 1972), that was signed and ratified by more than 90% of the world's countries, the risk of bioterrorism is as real as the risk of pandemic, of zooantroponosys, of exotic and tropical infectious and contagious diseases, etc., as it is with the recent epidemic of Ebola.[5] As a result, the WHO, the EU and NATO recommend concrete measures for decreasing those risks and for increasing the response capacity of each country, of the alliance and of the international community.

Given the EU's recommendations to operationalize at least 40 P4 laboratories within the member countries, to be designed and operated under standardized WHO conditions, the project responds to international demands and also to the national interest.

The operationalization of an integrated research and expertise platform for biological warfare and bioterrorism agents is relevant to the approached scientific field, following the **state of the art** (current stage) character of the research in the field of protection against biological agents, by implementing internationally used modern techniques. The project is based on implementing **cutting edge** technologies for diagnostic, prophylactic pre-exposure and post-exposure, cure and recovery, aspects regarding the action mechanism in infectious diseases, the therapeutic means to counteract the effects of biological agents and the epidemiological surveillance.[6]

Internationally, there are concerns regarding the achievement of a coherent system of epidemiological warning and intervention, the project being in line with the world situation. Designing and equipping the platform according to international recommendations determines that the level of performance of the proposed infrastructure must be internationally

competitive and must take an active role in the global effort of health protection against biological agents.[7]

Our concept for the operationalization of the Integrated Platform of scientific research and expertise of war and bioterrorism biological agents.

Creating the Integrated Platform will allow the defensive scientific research and medical expertise for weapons/biological agents and for the diagnosis of people infected with particularly dangerous biological agents, and for the medical intervention in epidemics or biological attacks.[8,9,10] It involves, in the first stage, monitoring the continuation and completion of the upgrading and rehabilitation of buildings, installations and perimeter security measures, including strengthening the capacity of health protection against biological weapons, bioterrorism and particularly dangerous biological agents.

It is important to liaise with specialized companies (selected not only by public tenders) within the allocated funds, for the execution of the Integrated Platform, for doing the reception at the time of commissioning the modernized Laboratory of Microbiology (declared at the UN as being under construction) for in vitro analysis, and for doing the reception at the time of commissioning the modernized Biobase, for in vivo analysis as well as for complementary analysis of analytical and experimental toxicology, neuro-psycho-pharmaco-logy, bio-pharmacy and the related logistical and security support.[8]

Taking into account the unique nature of this facility on national and regional level, as well as the direct and indirect costs related to the spatial planning, maintenance, and exploitation of this advanced technology objective, we rethought the configuration and the operation of the component objectives for maximum efficiency.[8] Thus, the facility can provide, through its equipment and operation, not only the scientific research and expertise for ABR, bioterrorism and biocrime, but it can also become practically involved in the epidemics/ pandemics or zoonoses with exotic and tropical diseases, that can occur as major emergencies, as is the recent Ebola outbreak. This facility with a maximum level of biosafety can also serve for other specific activities with major risk level; for example, with chemical warfare agents (CWA) or accidents with toxic industrial chemicals (TIC), with radiological warfare agents (RWA) or accidents with radioactive substances, or for any other extremely dangerous substances (HazMat). Changing destination can be achieved operationally, whenever necessary, even if it is one day to another, by replacing the work team with specialists from the DM/MND structures, according to the new destination and by replacing the specific equipment: removing from the highly secured working chamber of the equipment and materials which are no longer needed (through the decontamination airlock outlet) and inserting those that are necessary to the new mission. However, inside the work chamber, materials deposits are not stored for in vitro analysis. These are found in the "hand deposit" of the laboratory, inside the units' deposit or are purchased by emergency from different sources.[8,9,10] At the same time, the Biobase for test animals can serve all military medical laboratories due to the fact that it is conceived to immediately adapt to new requirements for different animal species. In terms of the annex facilities and amenities, they are basically for general purposes, for every type of medical laboratory and they inclusively ensure the proper functioning of the entire facility in which the integrated Platform is found. The platform can be adapted without structural changes to the CBRN agents of any kind, either separately or combined.

The integrated platform for the scientific research and expertise of bioterrorism and biological warfare agents contributes to strengthening the capacity of scientific research of DM/MND for the expertise of WBA/CBRN agents. During biological crisis situations, it can strengthen the National Healthcare System in terms of providing a microbiological diagnostic to the sick or suspected to be sick or to the animals, as well as for the detection, identification and confirmation of CBRN agents under biosafety and biosecurity conditions.[11,12] The facility, as a medical-military objective, can be useful interdepartmentally: Ministry of National Defense (MND), Ministry of Health (MH),

Ministry of Agriculture and Rural Development (MARD), Ministry of Internal Affairs (MIA), Ministry of Justice (MJ), Ministry of Environment, Water and Forests (MEWF) and Romanian Intelligence Service (RIS).

Studies and procedures for the operationalization and integration of the Laboratory of Microbiology and of the Biobase.

The integrated platform consists of complementary elements acting in algorithm: the Microbiology laboratory for in vitro analysis, the Biobase for in vivo analysis, the Mobile team for biological intervention (EMI-Bio) for field activities, as well as the annex utilities for the proper functioning of the objective.

The design, the feasibility study and the outline design for the Integrated platform of the scientific research and expertise of war and bioterrorism biological agents also includes the update of the previously modernized objectives, during 2007-2009 (Laboratory of Microbiology and Biobase), as well as the utilities and Annex facilities. The commissioning of the installed equipment and staff training with accredited supplier firms must be supplemented by specific new latest technology purchases. The explanatory memoranda and the feasibility study for the operationalization of the integrated platform are necessary because the financial burden is very high and must be quantified because the investment proposal submitted to the policy makers needs to be supported by the necessity and the opportunity of the investment.[8]

The activity of verifying the conditions related to the authorisation, the qualification, the certification and the accreditation of the Integrated platform for scientific research and expertise of biological agents

- The activity of verifying the conditions related to the authorisation of the Integrated platform. The process of modernizing the two objectives was carried out under the guidance of the National Authority for Scientific Research and Innovation (ANCSI) after attending the PNCDI Capacities national competition and after obtaining government funding through the Ministry of Education in 2007. As required by the investor, existing complementary objectives were selected: a laboratory of virology and the vivarium. ANCSI monitored the design, development and the endowment with installations and equipment of modernized objectives and performed the final inspection for the reception of the works, in 2009. The report prepared by ANCSI concerns only the fulfillment of the specific research and acquisitions objectives. Depending on the technical characteristics of the newly installed equipment, the owner must provide the utilities: electricity, cold water, hot water, distilled water, sewage, lighting, ventilation, heating, security, specific supplies and specialised staffing.

After the rehabilitation works to the building and installations have been completed, the Verbal Proceeding for the works reception will be issued. Next, follows the sanitation stage of the premises, of authorization and of commissioning the specific equipment and devices, by specialized companies and suppliers. Next, will be purchased consumables, reagents and inventory objects for the endowment of laboratories, depending on the tasks.

After establishing work teams with qualified and specialized staff follows the stage of drawing up the Verbal Proceeding for the functioning status of the Laboratory (through self-assessment and internal auditing). The Technical file for the authorization of the objective that contains data about the space, the endowment, about the staff and the work procedures is submitted to the Territorial Center for Preventive Medicine (TCPM/DM) in view of the sanitary authorization inspection of the objective.

After obtaining the sanitary functioning authorization, that involves the prior solving of the rehabilitation at the level of the entire facility, immediately will be performed a recheck of the qualification, certification and accreditation conditions of the Integrated platform for scientific research and expertise of biological agents.

- The verification of the qualification conditions of the Integrated platform, according to the Guidelines head. 7, p. 44-45: "Recommendations for the qualification of the laboratory and its facilities." The qualification of the laboratory/its facilities may be defined as a systematic process of examination and

documen-tation, demonstrating that the structural elements of the laboratory and of the systems and/or of the system components have been installed, inspected and tested, in terms of their operation, in conformity with the national and international standards.[2]

The laboratories designed to correspond to the Biosafety Levels 1 to 4, have different qualification requirements, with increasing levels of complexity. The geographical and climatic conditions, such as moisture or extreme temperatures, can also affect the laboratory structure, and thereby, its qualification demands. Once the qualification process has been completed, the significant structural components and the related systems will be subject to various conditions, including working conditions, under imposed conditions, logically possible, that will only thereafter be approved.

The qualification process and the acceptance criteria will have to be established from the design phase, of construction and/or renovation. By knowing the qualification requirements from the very beginning, the staff (the architects, engineers, the staff responsible for the safety and health assessment, as well as the staff of the laboratory) will be able to better understand the performance that has to be achieved by the laboratory.

The qualification process provides the institution and the community within which it operates a higher degree of confidence, given the fact that the structural elements, the electrical systems, the mechanical and drainage systems, the insulation and decontamination systems, as well as the security and alarm systems will function as initially designed, ensuring secure handling in the laboratory or in the biobase of any potentially dangerous microorganism.

The qualification activities are generally performed, from the design stage, continuing as such during the construction and installation of the laboratory and its facilities and during the warranty period, which should cover at least one year after its entry into service.

The agent assessing the qualification, acts as a guide for the institution that is building and renovating the laboratory and must be considered as a member of the concept team, his early involvement in the project design being essential. The institution may act as its own qualification agent, if it has a trained auditor. In the case of more complex laboratory facilities, with biosafety level 3 or 4, the institution may use the services of a qualification agent outside the institution, with proven experience in the successful implementation of the qualification of laboratories and biobases with complex levels of biosafety. When referring to a freelancer qualification agent, representatives of the institution will also participate as team members: the safety officer at institution level, the project manager, the program manager and a representative of the technical service's maintenance and intervention.

A list will exist to work with, consisting of the laboratory's systems and of the components that will be included in the qualification plan, for testing the functionality correlated with the degree of securing the facilities to be built or renovated. This list is not exhaustive, being adapted to the laboratory specifics. Clearly, the actual qualification plan must reflect the complexity of the respective laboratory.

- The verification of the certification conditions of the Integrated platform according to the Guideline head. 8 p. 45-60: "Recommendations for laboratory certification and its facilities"; it is similar to the qualification, but is run by a committee of national experts approved (the Ministry of Health, RENAR, the National Association of Medical Laboratories etc.). The WHO model questionnaire list, shall be completed during the certification inspection, in the presence of the institution's representatives, who know the objective.[2]

- Verification of the accreditation conditions of the Integrated Platform.

The Ministry of Health is able to grant accreditation only up to the P3 level; so, after reaching this level, the next step would be to resort to an international organization (WHO, EU, ECDC, NATO etc.), if an accreditation at maximal level is required and if all the required conditions are fulfilled and whether there is adequate funding.[7]

The complexity of running operations in a laboratory with maximal biosafety, exceeds the scope of the Biosafety Guidelines. More details and information can be found in the O.M.S. Biosafety Programme (according to the Biosafety Guidelines, Annex 3). The available information related to the training courses and to the profile information materials can be obtained by written request, for example from the Biosafety programme, Department of Communicable Disease Surveillance and Response, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (http://www.who.int/csr/).

Basically, the activity of verifying the conditions related to the authorisation, the qualification, the certification and the accreditation of the Integrated platform for scientific research and expertise of biological agents ascertains whether the objectives satisfy the requirements and proposes the accreditation. If the requirements are only partially met, then the nonconformities will be recorded and the inspection will be effectively resumed when all rehabilitation works to the platform's components will be completed. Only then, the laboratory may be declared fully functional at the highest level of biosafety. If all the imposed requirements cannot be met, or in the meantime the requirements for biosafety are amplified and the facility no longer meets the new requirements, then the facility can be accredited to a lower level, adding additional equipment for biological protection or other appropriate measures, whenever necessary.

OBSERVATION

Following an increase in the capability requirements concerning laboratories, we have provided in the design concept new technical parameters of the platform and the integration of new compartments with related activities of toxicology, pathology, neuropsycho-pharmacology, biopharmacy, micro pharmaceutical, specific testing activities, etc. However, the new facility does not allow, in terms of spaces and technological flows, their permanent dislocation in the space of the integrated Platform. If the dislocation of any other laboratories is needed, other spaces must be designed, built and purchased that correspond to international standards in the field, disseminated by the Ministry of Health.

Executing the integrated platform, its operationalization and, implicitly, the investment's financing is required in order to meet the requirement of the E6218 Capability Target, as a collective CBRN defense/ protection facility and military-medical scientific research for CBRN medical protection.

The original concept of ABR and bioterrorism scientific research and expertise was completed over time, in consultation with the colleagues from other specialties who are involved in CBRN medical protection and related areas of expertise that are complementary to the basic activity, in order to work under biosafety conditions, in full compliance with international norms.

CONCLUSIONS

The existing upgraded objectives should be operationalized so as to fulfill the targeted purpose: scientific research and expertise of biological agents and biological weapons, for in vitro and in vivo analysis. A laboratory with a maximal biosafety level allows working with any high risk agents, being versatile. We also provided new compartments with related activities to toxicology, radiobiology, anatomic pathology, neuro-psycho-pharmacology, biopharmacy microproduction and specific testing etc. The general concept enables the collaboration/cooperation of all CBRN medical protection laboratories and the cooperation with other military, civilian, national and international entities: NATO, EU or CIMIC.

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