



Comparative Analysis of Biosafety Guidelines of the USA, WHO, and Russia (Organizational and Controlling, Medical and Sanitary—Antiepidemiological Aspects)

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Abstract

Carrying out research for the purpose of prophylactic medicine with dangerous, highly infectious causative agents of disease requires appropriate safety conditions. In addition, the need for appropriate biological safety and security considerations is acquiring an ever-growing national and international importance given the existing threat of the use of these agents by terrorists. Because of these facts, the harmonization of national safety guidelines regulating the organization and work with Hazard Group I-IV pathogens in different countries is gaining more importance and relevance. This paper presents a comparative analysis of safety guidelines and regulations from the United States contained in the Centers for Disease Control and Prevention-National Institutes of Health Biosafety in Microbiological and Biomedical Laboratories (BMBL), the World Health Organization Laboratory Biosafety Manual (WHO LBM) and Russia's Sanitary Rules (SRs).

Introduction

Carrying out research for the purpose of prophylactic medicine with dangerous, highly infectious causative agents of disease requires appropriate safety conditions. Given the growing scope of international cooperation in this field and the exchange

of work between scientists, there is an ever-growing national and international importance. These facts, along with the reality of existing threats from the use of highly dangerous pathogens by terrorists and the need for appropriate biological safety conditions for work, and storage and transportation of these agents, have drawn attention to the increased global importance of, and relevance to, the concept of harmonization of national biological safety guidelines that regulate work with Hazard Group I-IV pathogens in different countries. The need to develop national and joint international contingency programs for possible bioterrorist attacks also makes harmonization necessary. The comparative analysis of biosafety guidance of the USA, the WHO, and Russia carried out at SRC VB "Vector," and the development of recommendations and proposals based on these analyses to be included in the new edition of the Russian *Sanitary Rules*, could be regarded as the first step in this direction. The urgency and practical value of this work for SRC VB "Vector" are explained by the fact that the Center is one of 17 Russian official institutions possessing specialized collections of Hazard Groups I-IV microorganisms. In particular, the Center possesses a collection of Hazard Groups I-IV viruses and is a WHO Collaborating Center for diagnosing orthopoxviral infections. In addition, a repository of smallpox virus strains and

DNA was founded and is functioning. A large number of cooperative research projects and programs such as the Russian-American smallpox program are being carried out within the scope of international cooperation.

Comparative Analysis

A comparative analysis of the Russian SRs (SRs 1993, 1994, 1999, 1996), the U.S. BMBL (CDC-NIH, 1999), and the WHO LBM (WHO, 1993) has been conducted. The comparative analysis found differences among these documents including organizational, regulatory medical, and antiepidemic aspects, which have been identified and are listed below:

- Technical execution of the documents
- The status of the documents
- The content and volume of the documents
- The system of obtaining permission to work
- The classification of pathogenic microorganisms
- Biosafety levels for working with laboratory animals
- The requirements and control of admission of personnel to work with biological material
- Personal responsibility for working with biological materials
- Shipment and transfer of biological agents
- Contingency plans and emergency procedures
- Risk assessment
- Primary and secondary containment barriers
- Organization of training

Technical Execution and Arrangement

Analysis of these documents revealed differences concerning their technical execution and arrangement. Biosafety issues, recommendations, and solutions are considered in four separate Russian SRs regulating various biosafety aspects, while in the BMBL and the WHO LBM guidelines, they are presented as integral documents (SRs 1993, 1994, 1999, 1996; CDC-NIH, 1999; WHO, 1993).

The Status of the Documents

The SRs, BMBL, and LBM have differences in their regulatory status and emphasis. The SRs are regulations (sanitary norms) that are considered

mandatory by any institution regardless of the department it refers to or the form of the property. Disciplinary, administrative, and criminal proceedings can be instituted against organizations violating these SRs. The BMBL, however, is a guideline that provides the best recommendations for application of safety practices and risk assessment and is of particular importance in providing guidance in the building of new laboratories or remodeling existing ones. In the United States, the BMBL is utilized for regulatory purposes to evaluate a facility's suitability for working with "Select Agents," which are pathogenic agents that have been placed on a restricted transfer and possession list in the United States because of their potential use as a biological weapon for terrorists. Besides those for "Select Agents," these recommendations also play an advisory role rather than being a regulatory obligation. The BMBL was developed as an advisory guideline and, in the opinion of the authors, should be updated to provide clear regulatory guidance. The WHO LBM has a more practical role, contains reliable information, and is a compact and convenient directory for practical use.

The Content and Volume of the Documents

The next group of differences concerns the content of the documents. The BMBL contains individual sections on risk assessment, a brief description of the characteristics of the infectious agents, and appendices that describe the biosafety cabinets which the SRs lack. The risk assessment allows for the development of different facilities and establishes various procedures for different levels of risk when working with the same agent based on the procedures used. For example, there is generally a lower risk working with a diagnostic specimen of a pathogenic agent than working with the same agent in aerosol format.

The BMBL also contains the following sections which are not present in the SRs or the WHO LBM:

- A separate list of highly dangerous animal pathogens
- Reference material, including addresses for obtaining additional information;
- Materials on immunoprophylaxis
- Physical safety in microbiology and biomedical laboratories

- An integrated pest management (IPM) program for pest management (e.g., flies and cockroaches)
- Principles of work with toxins of biological origin
- A description of work with human and non-human primate cells and tissues

The WHO LBM (WHO, 1993) contains the following sections (or appendices) which are not included in the SRs (SRs, 1994, 1999, 1996) or the BMBL (CDC-NIH, 1993):

- A description of laboratory equipment
- Chemical, fire, and electrical safety, as well as requirements for the training of personnel and a training program
- A safety checklist
- Separate material on personnel immunization and educational information on microbiological safety

The SRs (1994, 1999, 1996) contain individual sections (or appendices) which are not contained in the BMBL (WHO, 1993) or the WHO LBM (WHO, 1993) on:

- Procedures for catching, transporting and maintaining wild vertebrates for carrying out experiments
- Work in hospitals, isolation wards, and observation rooms
- Medical surveillance of the population
- Disinfection and pathologoanatomical work in the foci of highly dangerous infectious agents
- A procedure for employees leaving institutions working with biological materials
- Disinfection devices and methods used in the work with pathogenic microorganisms
- Decontamination procedures for different objects contaminated with pathogenic microorganisms
- Chemical tests for controlling temperature parameters of the function of steam sterilizers
- A bacteriological method for controlling steam sterilizer efficiency
- A procedure for the replacement of HEPA filters in an exhaust ventilation system and determination of their efficiency
- Requirements for testing contaminated media in mobile disinfection chambers
- Requirements for testing sewage water for pathogenic microflora

However, in contrast to the WHO LBM, the SRs do not have separate sections (appendices) on

chemical, fire, and electrical safety; training of personnel and a training program; safety checklist; or educational information on microbiological safety (SRs 1994, 1999, 1996; WHO, 1993).

The SRs also have separate annexes that describe the functions and scope of activities of the commission that regulates the observance of biological safety requirements at the institution (enterprise). In contrast to both the BMBL and the WHO LBM, the SRs describe in detail the procedure for interested institutions to obtain permission to work with Hazard Groups I-IV microorganisms and recombinant DNA molecules from the bodies of the State Sanitary-Epidemiological Inspection Committee of the Russian Federation, as well as the necessary requirements and documents to obtain this permission. Standard permissions to work with Hazard Groups I-IV microorganisms and recombinant DNA are given for a period of 5 years, while work with aerosols is given for a period of 2 years (SRs 1993, 1994, 1999, 1996).

In contrast to the SRs, the WHO LBM lacks individual sections (or appendices) on procedures of catching, transporting, and keeping wild vertebrates for use in experiments; work in hospitals, isolation wards, and observation rooms; medical surveillance of the population; and disinfection and pathologoanatomical work in the foci of highly dangerous infections. In contrast to the U.S. BMBL, there are no sections (appendices) on risk assessment, the brief characteristics of infectious agents, a listing of highly dangerous animal pathogens, complex programs for pest management, descriptions of work with human and primate cells and tissues, and principles of work with toxins of biological origin (SR 1993; SR 1994; SR 1999, CDC-NIH, 1999; WHO, 1993).

Based on the above information, it is evident that there are significant differences in the content of the three documents reviewed. The analysis shows that there are far fewer differences between the BMBL and the WHO LBM than there are between the SRs and the BMBL and WHO LBM. However, on the whole, these differences neither hinder the understanding of these documents nor lower their practical value. Nevertheless, we consider it expedient to supplement the SRs with the missing sections and materials.

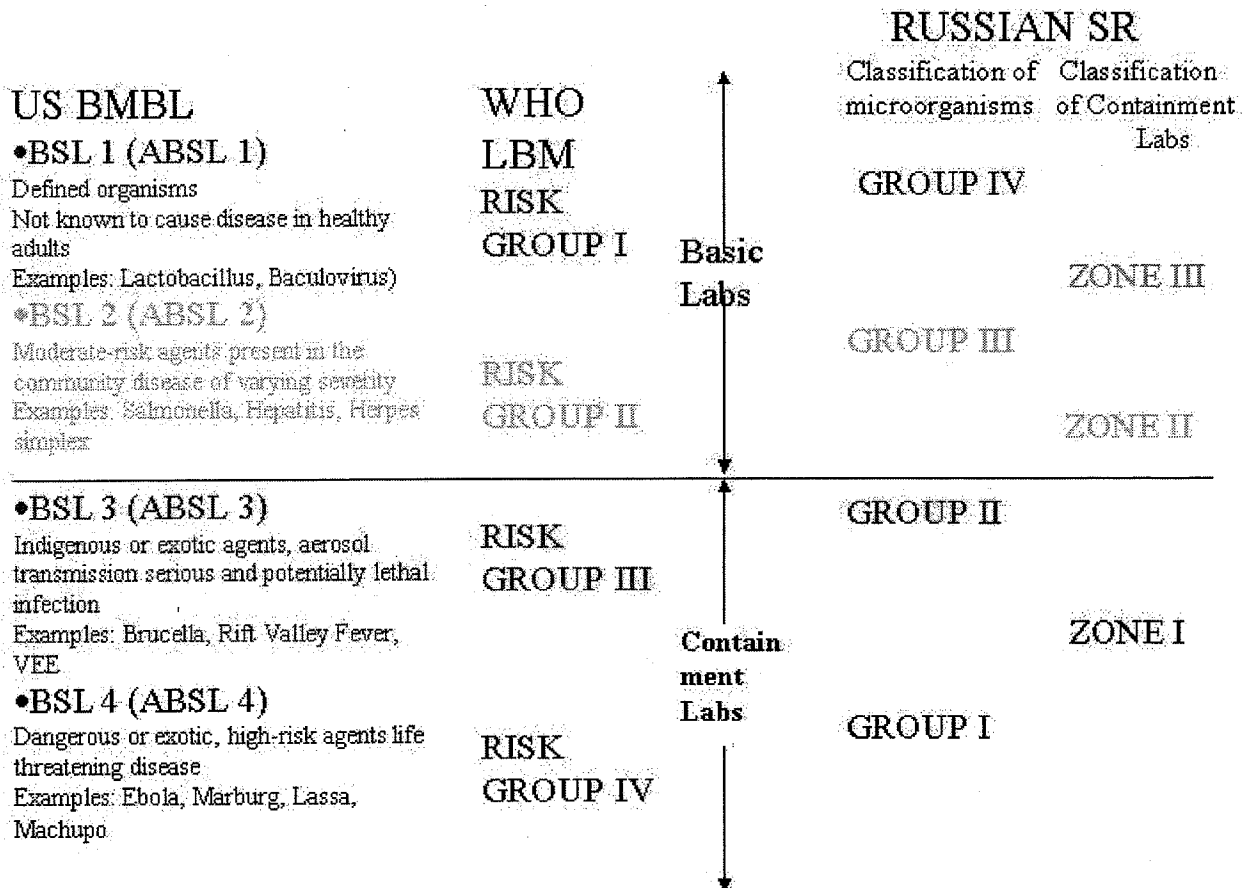
The System of Obtaining Permission to Work

In contrast to the U.S. BMBL and the WHO LBM, the SRs describe in detail the procedure for interested institutions to obtain permission to work with Hazard Groups I-IV microorganisms and recombinant DNA molecules from the organs of the State Sanitary-Epidemiological Inspection Committee of RF, as well as the requirements and documents necessary for obtaining this permission. Standard permissions to work with Hazard Groups I-IV microorganisms and recombinant DNA molecules are given for a period of 5 years, while work with aerosols Hazard Groups I-IV microorganisms is given for a period of 2 years (SRs 1993, 1994, 1999, 1996).

The Classification of Pathogenic Microorganisms

Figure 1 shows the differences among the Russian, WHO, and U.S. classifications of pathogens, which shows that the risk groups are reversed. In the Russian system of classification, Group IV is the least hazardous group while in the United States, Biosafety Level 1 (BSL-1) is the lowest risk group and in the WHO classification system, it is Risk Group I. Group I in the Russian system contains the most dangerous and exotic organisms while the U.S. system lists these agents as BSL-4 and the WHO as Risk Group IV. There are also differences between the Russian and U.S. systems in the individual classification of microorganisms within the hazard groups.

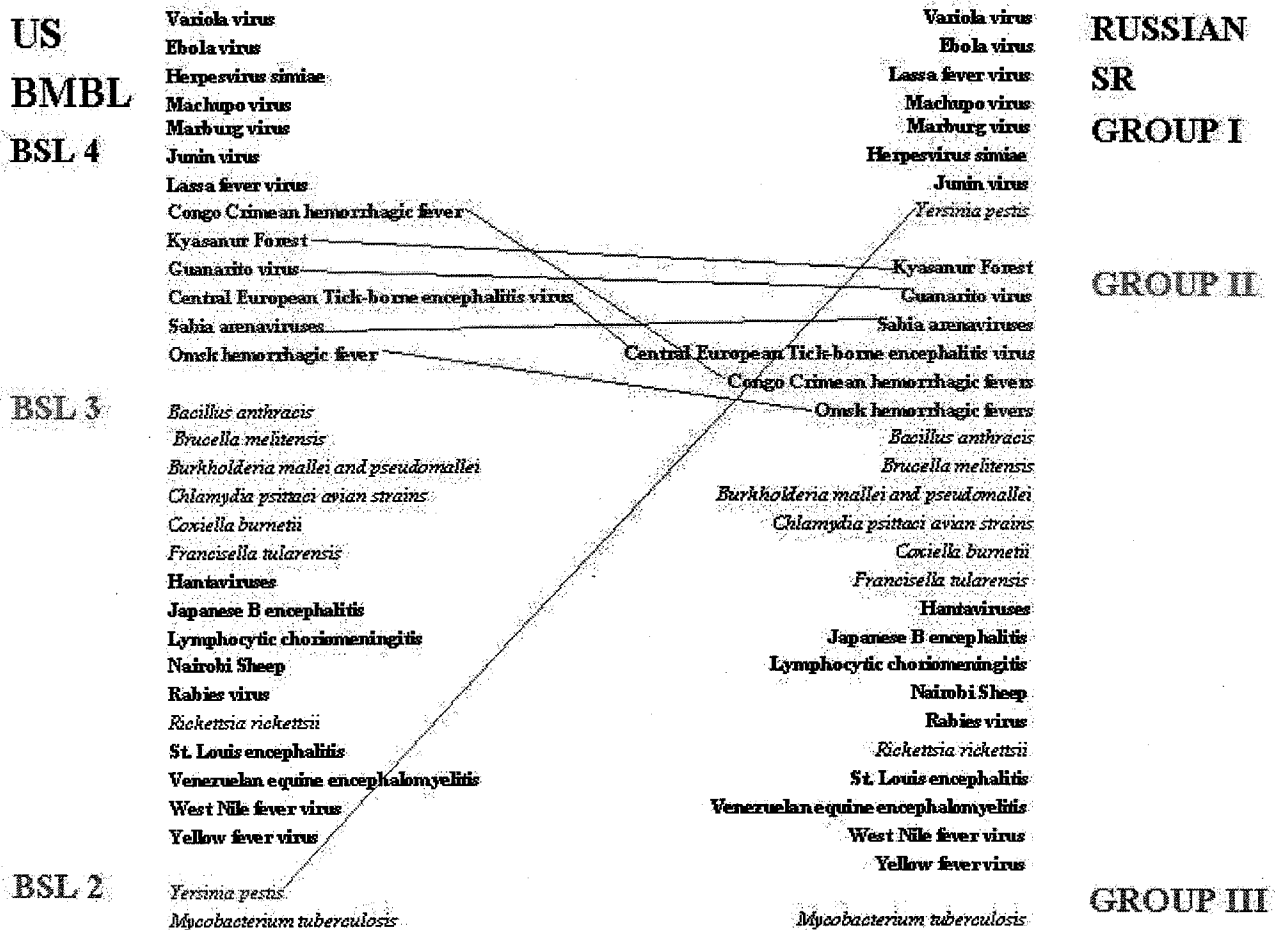
Figure 1
Risk Group Comparisons



The same microorganism may be classified under different groups (Figure 2). For example, the causative agent of tuberculosis is listed as a BSL-2 pathogen in the U.S. BMBL while the SRs list it as a Group III hazard. Similarly, the agents of Congo-Crimean hemorrhagic fever, Omsk hemorrhagic fever, and Central European tick-borne spring/summer encephalitis are all listed as BSL-4 pathogens in the U.S. BMBL, while the Russian CRs lists them as Group II pathogens. It should also be noted that in the U.S. BMBL *Yersinia pestis* can be classified either under BSL-2 or BSL-3, depending on the risk level (e.g., the potential for droplet or aerosol production, work with antibiotic-resistant strains, or the use of large quantities or high concentrations of infectious materials). This situation considerably hin-

ders any mutual understandings when international research groups carry out collaborative projects. In view of this, we prepared recommendations for a new edition of the SRs for the State Sanitary-Epidemiological Control of the Russian Federation, to include matching the numeration of pathogens in the Russian classification with those in the international classifications. Furthermore, it was also recommended that tuberculosis pathogens (with multi-drug resistance) be classified into Hazard Group II which includes more dangerous pathogens, instead of Hazard Group III where it is now located. Additionally, monkeypox virus, which is listed as a BSL-2 pathogen in the BMBL, is not even listed as pathogen in the SRs (SRs 1994, 1999, 1996).

Figure 2
Agent Classification Comparison



The SRs (Figure 1) contain three biosafety levels (zones) instead of four. The numeration and distribution by risk level are reverse to those in the American and international classifications. We prepared recommendations concerning the change of numeration of biosafety levels in the Russian classification by the degree of danger—from the 1 to 3 (from the absence of hazard to high danger). These recommendations were submitted to the State Sanitary-Epidemiological Control of the Russian Federation. The introduction of biosafety level 1 in the U.S. BMBL and Risk Group I in the WHO, which are used for work involving well-characterized agents not known to cause disease in healthy adult humans, is practically analogous to biosafety level 2 and Risk Group 2 and, in our opinion, is somewhat artificial. The presence of this level not only erodes the borderline between these two levels, but also hinders the process of forming a clear line of qualitative transition from low biosafety levels to higher ones. Students and laboratory workers should feel a multiple increase of danger (risk) and responsibility for themselves and the surrounding community when working with pathogens at higher risk levels. The level of the “clean” zone (the 1st zone in the new SRs, which would be equivalent to the current BSL-1 or RG-I) would be a solution for the problems mentioned above (SRs 1994, 1999, 1996; CDC-NIH, 1999; WHO, 1993; Stavskiy, Hawley & Crane, 2002).

Biosafety Levels for Working with Laboratory Animals

In the SRs, animal studies are not classified separately as they are in the U.S. BMBL, which classifies animal studies into Animal Biosafety Levels (ABSL-1, ABSL-2, ABSL-3, and ABSL-4) based on the degree of hazard. According to the SRs, the primary and determining factors for work with animals is the degree of hazard posed by the microorganism being studied (SRs 1994, 1999) and the work with animals infected with Hazard Groups I-IV (SRs) is performed only under conditions of the “dirty” zone (1st zone). Safety requirements and recommendations for organizing animal studies under conditions of the 1st zone are analogous to those of the U.S. ABSL-1 though ABSL-4. Unlike the U.S. BMBL and the

WHO LBM, the SRs also consider requirements for organizing and carrying out work with animals and ectoparasites under field conditions (procedure for catching, transportation and analysis) (SRs 1994, 1999, 1996; CDC-NIH, 1999; WHO, 1993; Stavskiy, Hawley & Crane, 2002).

The Requirements and Controls for Admission of Personnel to Work with Biological Material

The requirements and controls for admission of personnel to work with biological material are described in more detail in the SRs than the U.S. BMBL or the WHO LBM. The work with Hazard Groups I-IV pathogens requires:

- Higher or secondary medical, biological, or veterinary education and special training
- The permission of the director of the institute to take the job
- The absence of contraindications against vaccine prophylaxis and treatment with specific preparations
- A medical examination before taking the job
- An annual medical examination during employment

Permission to work with experimental material is given by the order of the director of the institute every 2 years after checking the individual's knowledge of safety. Engineering and maintenance staff, as well as disinfecting and cleaning personnel, are trained within the department and permitted to work in accordance with the official duties and institutional order. The director of the institute gives temporary engineering and technical personnel permission to enter the laboratory. These personnel can visit the laboratory only after cessation of work and disinfection of the laboratory and only if accompanied by a department employee. The visit is then recorded in a registry. Temporary specialists (medical and veterinary doctors, biologists, etc.) are admitted to the rooms where biological material is handled only after receiving written permission from the director of the institute. The purpose of the visit is also recorded in the registry. Employees who come in contact with biological material of Hazard Groups I-IV pathogens need to be vaccinated prior to working with these pathogen (with the exception of *Vibrio cholerae*). Those individuals having contraindications for vaccination are permitted to work only with a

special institutional order. Additionally, individuals having contraindications against vaccination are not permitted to work in aerosol laboratories or with material infected or suspected of being infected with the causative agent of Q (*Coxiella burnetii*) (SR 1994). Only specialists who hold higher and secondary education experience and who have appropriate training are permitted to work with Hazard Groups I-II pathogens (SR 1999). All employees working with Hazard Groups I-IV pathogens must undergo daily medical surveillance with thermometry (temperature check for fever), except those working with *Vibrio cholerae* and toxins of biological origin. The medical surveillance results are then recorded in a special registry and signed by a responsible doctor (or scientific worker). For individuals working with the *Vibrio cholerae* pathogen, obligatory tests for vibrio-carriage are required if the individual exhibits gastroenteric malfunctions. All employees working with Hazard Groups I-II pathogens are set up to receive a regular medical evaluation. Each employee must inform the director of the institute or an official on duty about any illness or adverse medical symptoms before continuing to work. The institution's doctor would be sent to the home of the ill employee for an epidemiological investigation and to determine the need for isolation. The result of the visit is recorded in a registry and reported to the director of the institute. The visit of a private doctor of the general medical system is allowed only after that of the institution's doctor; critical care indications are an exception and doctor care is allowed under these circumstances. The patient and his or her relatives would be required to inform the doctor from the general medical system about the nature of the patient's work and also to inform the head of the department where he or she works about the incident. Employees who cannot come to work for some reason are required to inform the head of the department within 2 hours of when they are expected to report to work. If an employee does not come to the institution 2 hours after his or her normal start time and nobody knows where he or she is, the head of the department must take the necessary measures to learn where the employee is and why he or she is absent from the workplace (SRs 1994, 1999).

The U.S. BMBL and WHO LBM requirements

for permission for the scientific, engineering, and maintenance and support staff to work with biological materials are as follows:

- Special training in the recognition of disease and handling of pathogens
- A medical examination before taking or changing a job
- Medical surveillance during employment controlled by the head of the laboratory

In addition, a risk assessment should be conducted to determine when vaccination is obligatory (mandatory) or recommended, what samples should be taken for analysis, and the type of medical examination of personnel to be performed.

The head of the laboratory is responsible for:

- Controlling access to the laboratory and restricting access to designated personnel
- Organizing and carrying out laboratory activities
- Instructing all laboratory and support staff concerning any potential risk factors relating to the work being conducted
- Informing laboratory staff about appropriate biosafety precautions
- Ensuring that procedures are in place to check for contamination
- Revising the instructions for work with biohazardous agents annually
- Organizing additional instructions and training of personnel

According to the WHO LBM, personnel working with pathogens of Risk Groups III-IV (international rating system) should have a special card certifying that they are working with these agents. The card should indicate the names of the head of the laboratory and the consulting doctor or safety officer (Stavskiy, Hawley & Crane, 2002).

The SRs describe a clearer and more rigid system of requirements and controls to admit personnel to work with biological material and request medical aid than either the U.S. BMBL or the WHO LBM. This allows for taking timely emergency therapeutic and antiepidemiological measures (within several hours). All the personnel performing a cycle of work with Hazard I-II pathogens (Russian classification) are surveyed by the Biosafety Service every 24 hours, both during the working hours and after work (a more rigid system of requesting medical aid, prompt

measures taken if an employee does not come to work, etc.). The U.S. BMBL and the WHO LBM do not contain rigid requirements about medical control after the working day.

Personal Responsibility for Working with Biological Materials

As the analysis has shown, the SRs contain a rather complete description of a structure for distributing responsibility among all personnel participating in organizing and carrying out work with infectious materials. However, in contrast to the U.S. BMBL and the WHO LBM, nothing is said about the responsibility of personnel subordinate to the head of laboratory. This is a serious flaw, especially in organizing and carrying out work with highly dangerous pathogens. According to the SRs and in contrast to the U.S. BMBL and the WHO LBM, the Commission controlling biological safety requirements is an executive and consultative entity that has a wider range of responsibilities compared to analogous structures described in the U.S. BMBL and the WHO LBM (SRs 1994, 1999, 1996; CDC-NIH, 1999; WHO, 1993).

Shipment and Transfer of Biological Agents

It should be noted by the results of this comparison that in contrast to the U.S. BMBL and the WHO LBM, the SRs consider in detail not only questions of shipment and transfer of biological materials but also registration and storage procedures for Hazard Groups I-IV pathogens including collections of cultures of microorganisms.

Documents regulating some important aspects of these activities obligatorily observed in the territory of Russia are presented as separate independent appendices to the Sanitary Rules: registration forms (18 forms); a list of causative agents of human, plant, and animal diseases (pathogens), their genetically modified forms, fragments of genetic materials, and equipment that could be used to develop biological and toxin weapons which are exported according to licenses (cited from the President's decree); a document on the control of procedures for exporting causative agents of human, plant, and animal diseases (pathogens), their genetically modified forms, fragments of genetic materials, and equipment that

could be used in the development of biological and toxin weapons; a classification of microorganisms that are pathogenic for man; a list of organizations possessing specialized collections Hazard Groups I-IV microorganisms; a certificate permitting shipment of special cargo (pathogens of Hazard Groups I-IV). In contrast to the U.S. BMBL and the WHO LBM, according to the Russian SRs, pathogens of Hazard Groups I-II are transferred and delivered within the country only by two special messengers. Pathogens of Hazard Groups I-IV are transferred abroad through the International Post Office. Figure 3 shows the packing, shipment, and transfer of pathogens of Hazard Groups I-IV within the country (metal containers of different sizes and shapes are used as secondary containers; wooden boxes or standard parcel boxes can be used as outer containers) (SRs 1994, 1999, 1996; CDC-NIH, 1999; WHO, 1993). The packing intended for shipment and transfer of pathogens of Hazard Groups I-IV abroad should satisfy international conventions and rules (Figure 3).

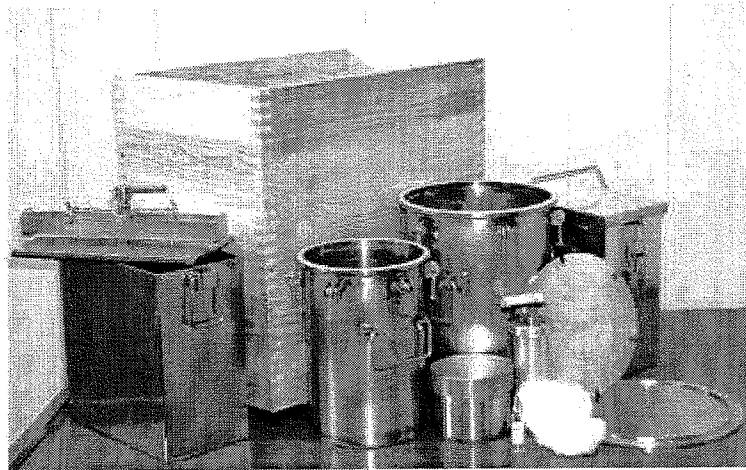
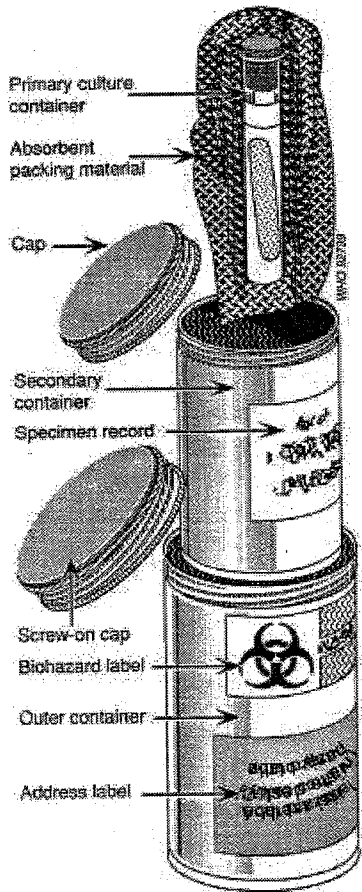
Contingency Plans and Emergency Procedures

A comparison of contingency plans and emergency procedures revealed that in contrast to the U.S. BMBL, the SRs and the WHO LBM contain a more detailed description of contingency plans and practical recommendations for emergency situations involving biological material. This makes it easier to further develop appropriate working instructions for microbiological laboratories. In addition, it is important, in our opinion, that the SRs contain a standard requirement for an isolation ward at any institution where work with causative agents of plague, cholera, glanders, melioidosis, deep mycoses, and highly contagious viruses of Hazard Group I are conducted. The availability of a specialized isolation ward provides injured individuals with qualified and specialized medical aid within the first hours after an incident (SRs 1994, 1999, 1996; CDC-NIH, 1999; WHO, 1993).

Risk Assessment

In contrast to the SRs and the WHO LBM, the U.S. BMBL contains scientific and methodical recommendations to correctly determine appropriate

Figure 3
Packing of Pathogenic Microorganisms and Types of Containers
Used in the U.S.A., European Countries, and Russia



biosafety levels when working with infectious agents using risk assessment procedures. Determination of a biosafety level is based on an evaluation of the facility, equipment, and procedures used during work with an agent(s). Neither the SRs nor the WHO LBM contains such a separate section. However, some microbiological laboratory activities involving high risks are mentioned in the SRs; these include centrifugation, lyophilization, work in aerosols chambers, and work with animals requiring special safety measures. The WHO LBM contains more detailed descriptions of safe laboratory techniques and procedures associated with various risks such as the generation of microbial aerosols. It should be noted that the selection of the biosafety level according to the SRs is strictly determined by the degree of

danger when handling the infectious agent. The placement of this agent in the classification of pathogenic microorganisms was determined by leading microbiologists, epidemiologists, and the State Sanitary Inspection organs of Russia through a comprehensive analysis of all of the properties and characteristics of the agent (as in the case of a complex of risk factors) including interaction of the agent with the host. That is why the biosafety level required to work with a certain microorganism is determined by its placement in each hazard group of the microorganism classification presented in the SRs. The SRs and this classification are revised periodically (every 5 years) using newly obtained scientific and practical knowledge. It should be noted that many sanitary rules are the basis of Russian laws in the fields of

social security, health service, ecology, etc. The latter fact should be obligatorily taken into account when planning and carrying out activities on harmonization and unification of national biosafety guidelines, as it will certainly slow down this process (SRs 1994, 1999, 1996; CDC-NIH, 1999; WHO, 1993).

Primary and Secondary Containment Barriers

In contrast to the SRs and the WHO LBM, in the U.S. BMBL the concept of primary and secondary containment barriers is introduced from scientific literature, while the SRs and the WHO LBM contain only some hints on the use of different devices to protect personnel and the environment. In contrast to the SRs, the U.S. BMBL and the WHO LMB describe detailed characteristics and uses of different classes of biosafety cabinets and other equipment (engineering controls). It would be expedient to supplement the SRs with this information, taking into account the ever-growing use of engineering controls in Russian microbiological laboratories (SRs 1994, 1999; CDC-NIH, 1999; WHO, 1993).

Organizational Training

In all the analyzed documents, little attention was paid to the necessity of training personnel in the rules of working safely in microbiological and medical laboratories. Only the WHO LBM contains special sections on personnel training and educational information. Surely the presence of analogous sections in the SRs would enhance their practical value.

Summary

The described differences among the Russian SRs, the U.S. BMBL, and the WHO LBM reflect national peculiarities in working with Hazard Groups I-IV microorganisms. These developed in each country or group of countries (e.g., European countries) over time and during the evolution of safe work practices with infectious microorganisms. These guidelines are not antagonistic to each other in principle. Each of these documents has its strengths and weaknesses. In an effort to harmonize and improve the guidance provided for working safely with these microorganisms, the authors of these documents may

wish to consider revising their current documents to include information (e.g., field safety, risk assessment, training requirements, etc.) from other guidance documents. Organization and management of a project of this magnitude might be considered by the American Biological Safety Association International Working Group.

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