Chinese Biosafety Laws and Regulations, Including Matters of Biosecurity and Oversight of Genetic Engineering Activities

Hu Longfei (MD, MPH), Xiang Dapeng (MPH, ML), Shi Yongxia (Ph.D.), Huang Jicheng (Ph.D.), Zheng Kui (BS), Hong Ye (MD, MS), Li Xiaobo (MS), and Xing Luqin (BS)[1]

Prior to the outbreak of severe acute respiratory syndrome (SARS) in 2002, China had many measures related to biosafety dispersed among departmental rules and standards related to work with pathogens, but specific biosafety laws and regulations did not exist. China's network of biosafety measures was not systematic, nor was it comprehensive, particularly for laboratory biosafety. After the SARS outbreak, the Chinese government further realized the importance of biosafety to Chinese and human development. The relevant departments of the Chinese government have since been paying close attention to biosafety matters, studying the problems of biosafety and the developments that have been taking place to improve biosafety around the world. The Chinese government began to reorganize, revise, elaborate, and update its laws and regulations on biosafety, some of which have been issued to keep pace with advances in science and technology. For example, some recent regulations are designed to manage genetic engineering research and also the development, testing, and production of genetically modified organisms.

China has therefore improved its biosafety management system with a series of regulations that concern different aspects of biosafety. In conjunction with a 2004 State Council umbrella regulation on biosafety, two additional national standards and several subsidiary standards addressing specific aspects of biosafety have been issued. By early 2007, the Chinese State Council and responsible institutions of government had announced and implemented a series of revised and new biosafety regulations and

[1] The lead author of this essay, Hu Longfei, is the director and chief epidemiologist at the Department of Health and Quarantine, Guangdong Entry-Exit Inspection and Quarantine Bureau, No. 66 Huacheng Avenue, Zhujiang Xincheng, Guangzhou City, Guangdong Province, China. A brief biography of Dr. Hu can be found in an annex to this report. Xiang Dapeng, Shi Yongxia, Huang Jicheng, Zheng Kui, Hong Ye, Li Xiaobo, and Xing Luqin are employed at Health Quarantine Laboratory, Technology Center, Guangdong Entry-Exit Inspection and Quarantine Bureau, No. 13 Gangwan Avenue, Huangpu District, Guangzhou City, Guangdong Province, China. Dr. Shi is the corresponding author. e-mail: syx0817@yahoo.com.cn. Tel: 86-20-82270685. Fax: 86-20-82270685.

standards[2]. The result is that China is on the verge of completely establishing and implementing an almost ideal system of technical biosafety standards and regulations.

The General Framework for Biosafety Management of Biomedical and Pathogenic Microbiology Laboratories

The State Council established and implemented China's principal overarching framework for laboratory biosafety with the "Regulation on the Biosafety Management of Pathogenic Microbiology Laboratories" on 12 November 2004. This regulation established the basic pattern of biosafety management for microbiology laboratories that work with pathogens and defined the duties of all pertinent government departments and requirements for biosafety laboratories in China. This regulation, which articulates clear laboratory biosafety requirements, is divided into seven chapters: 1) the general rule; 2) classification and management of pathogenic microbiology laboratories; 3) the establishment and management of pathogenic microbiology laboratories; 4) infection control in pathogenic microbiology laboratories; 5) supervision and management; 6) legal liability; and, 7) supplementary provisions.

This ordinance also defined, as shown in Table 2, governmental responsibilities for the management of laboratory biosafety in accordance with the functions of various government agencies. Within these overall areas of responsibilities, the duties are further divided between the relevant bureaus and offices in each of the departments named.

In terms of the infectious threat that a microorganism presents to an individual or the community, a pathogenic microorganism is rated in four grades, with the first risk group posing the most serious harm and the fourth group the least serious health risk. Laboratories are divided into four levels of biosafety containment according to the risk level of the pathogenic microorganism and national standards for biosafety laboratories. The construction and accreditation procedures for pathogenic microorganism laboratories and for their personnel must meet the requirements stipulated in the ordinance.

This ordinance also specifies the essential terms for the collection, packaging, transportation, storage, and destruction of an infectious or pathogenic microorganism.

[2] A comprehensive list of China's biosafety regulations can be found in the Appendix.

Table 2: Division of Responsibilities for Laboratory Biosafety within the Chinese Government.

Governmental Department	Area of Responsibility
National Development and Reform Committee	Overall laboratory planning
General Bureau of Environmental Protection	Evaluation and certification of the environmental impact of laboratories
Ministry of Construction	Establishment of the construction standards and inspection of laboratories to ensure construction quality
National Accreditation Board for Laboratories	Accreditation of a laboratory's biosafety equipment and management system
Ministry of Health	For experiments related to human health, approval of the laboratory and its planned experiments; corresponding biosafety oversight
Ministry of Agriculture	For experiments related to animal research and health, approval of the laboratory and its planned experiments; corresponding biosafety oversight

Moreover, the ordinance requires that laboratories have measures in place for infection control and treatment protocols in the event of an accident in the laboratory. Should an accident with serious consequences occur, the relevant governmental departments that have oversight responsibility for the aspect(s) of a laboratory's infrastructure and/or operational procedures found to be at fault will bear legal liability.

The Mandatory Standards for Laboratory Biosafety

The Ministry of Health and the Ministry of Agriculture, respectively, issued the "General Biosafety Standard for Microbiology and Biomedical Laboratories" on 3 December 2002 and the "Veterinary Laboratory Biosafety Guidelines" of 15 October 2003. This pair of standards focuses on biosafety operational procedures, laboratory cleanliness, and management. Penalties for noncompliance are not included in these standards. To clarify and strengthen these standards, a mandatory national standard was issued on 5 April 2004 and implemented formally on 1 October 2004. This standard, "Laboratories—General Requirements for Biosafety," is largely patterned on the World Health Organization's *Laboratory Biosafety Manual*.[3] This standard raised the overall

[3] The General Administration of Quality Supervision, Inspection and Quarantine and the Standardization Administration issued this standard base on *Laboratory Biosafety Manual*, 3rd ed. (Geneva: World Health Organization, 2004).

threshold for laboratory biosafety in China, resulting in the regulation of many aspects of laboratory biosafety, including management and construction principles, biosafety ratings, the disposition of the facility equipment, personal protection, and biosafety practices. The Ministry of Health and the Ministry of Agriculture also issued two major subsidiary regulations under this standard.

The containment level for a given laboratory is determined by the relative pathogenic and infectious risk of the organisms the laboratory works with and the strictness of the procedures taken to safeguard employees, the public, and the environment. Containment levels are rated in four grades, from biosafety level 1 (BSL-1) for the lowest containment safeguards to BSL-4 for the highest. The corresponding containment levels for animal biosafety laboratory one (ABSL-1) to four were also established. This standard confirmed the fundamental requirements and evaluation criteria for the four biosafety containment level facilities and regulates in detail laboratory biosafety practices and personal protection. The regulations in this standard apply to medical laboratories and also to all kinds of biosafety laboratories (e.g., teaching, production).

Additional Standards for Biosafety in China

"Methods for the Biosafety Environmental Management of Pathogenic Microbiology Laboratories," issued by the State Environmental Protection Administration on 2 March 2006 and implemented on 1 May 2006, concretely establishes a demand for an environmental impact appraisal for biosafety laboratories according to their containment level, which is divided into four grades. The environmental impact assessment should be carried out when a biosafety laboratory is being built, renovated, or expanded. This ordinance also points out the approval procedures for building a new biosafety laboratory, for renovating or expanding a BSL-3 and BSL-4 laboratory engaged in activities with highly pathogenic microorganisms, and for importing and installing a mobile or trailer-like BSL-3 and BSL-4 laboratory. The organization conducting the environmental impact appraisal should be qualified to do appraisals of BSL-3 and BSL-4 laboratories.

An existing biosafety laboratory should register its systems for pollution and waste control with the appropriate authorities and file regular reports for its discharges of waste water and waste gas. All biosafety laboratories should set up a system for the monitoring and appropriate disposition of all solid hazardous wastes. All hazardous wastes generated during the course of laboratory activities are to be collected in special-purpose containers qualified for hazardous wastes. The laboratory should have different kinds of hazardous waste containers depending on the type of hazardous wastes being generated (e.g., liquids, sharp objects, solids). In addition, the laboratory should provide a temporary storage cabinet or other receptacle suitable for the needed levels of hazardous waste. In a timely fashion, hazardous waste should be decontaminated inside the laboratory and then transferred to a nearby business licensed to dispose of hazardous waste properly. The frequency of a laboratory's decontamination activities will depend on the size of the facility and its biosafety level. BSL-3 and BSL-4 laboratories should decontaminate their hazardous wastes following each experiment, with a decontamination method (e.g., autoclave, chemical disinfection) appropriate for the type of waste generated. All handling and transfers of a laboratory's solid hazardous waste should be accomplished and documented according to Chinese laws on "Prevention of Environmental Pollution Caused by Solid Waste" and relevant regulations of State Lead Bureau for Environmental Protection.

Mandatory Construction Code for Biosafety Laboratories

The Ministry of Construction issued another mandatory national standard, the "Architectural and Technical Code for Biosafety Laboratories," on 3 August 2004 and implemented it on 1 September 2004. This standard was based on an extensive survey and study of relevant domestic and foreign standards that took into account widespread domestic experience in engineering and construction. The standard stipulates some technical requirements about construction layout and the structure and fitting of major features of the laboratory. The central component of the regulation concerns the laboratory ventilation system, and the standard specifies the appropriate ventilation approach, design, and construction to achieve the proper directional flow of air, including the system-wide ventilation schematic and the construction material to be used. Likewise,

the standard sets control principles for water supply and plumbing, gas supply, power distribution, automation, and fire control in the facility. In addition, the principles and methods of construction, testing, and examination, and certification of BSL-3 and BSL-4 laboratories are necessarily regulated.

Rules on Biological Safety Cabinets

Biological Safety Cabinets (BSCs) are designed to greatly reduce the airborne hazards (e.g., aerosols, gases, vapors, dusts) generated by the activities performed inside the BSC. Class I BSCs protect the workers from these hazards before workers can inhale those contaminants; Class II BSCs protect the workers, the work inside the cabinet, and the environment from the airborne hazards.[4] The State Food and Drug Administration and the Ministry of Construction are responsible for the two central regulations governing biological safety cabinets in China. These regulations are very detailed, but their main contents concern the design, manufacture, examination, testing, packing, transport, and installation of BSCs. These two regulations will play an important role in standardizing the market for BSCs in China. As Table 3 indicates, the State Food and Drug Administration's YY0569 and the Ministry of Construction's regulation JG170-2005 are modeled on the Standardized Committee of Europe EN12469: 2000 and the National Standards Institute NSF49-2002. For instance, the State Food and Drug Administration regulation YY0569 adopts the KI-Discus test from the European standard for BSCs, EN12469: 2000.[5]

While the Chinese regulations are patterned on European and American BSC standards, they also include improvements on those models. For instance, regulation YY0569 states the performance standards for BSC, including an instant display for air

[4] Class III BSCs also exist for work with highly infectious pathogens and are totally contained, without a front opening. Negative air pressure is maintained inside the BSC, an airlock is used to bring materials into the BSC, and work inside the BSC is performed using ports with flexible gloves.

[5] The KI-Discus test is designed to allow measurement of how well the BSC will protect individuals who are using it. A disk containing potassium iodide is placed inside the BSC and generates an aerosol when it is made to spin. For a specific period of time, the air outside of the front opening of the BSC is sampled and analyzed to see how many potassium iodide particles can be detected. For example, a BSC is considered to provide good protection if no more than 1 particle from every 100,000 potassium iodide particles released inside the BSC can be detected outside of the BSC.

exchange rate and the air intake and an audio and visual warning system to alert workers to performance malfunctions of the BSC.

Table 3: Chinese Regulations Governing Biological Safety Cabinets.

Chinese Authority Overseeing the Standard	Identification Number of the Standard	Date Issued	Date Implemented	Models for the Standard
State Food and Drug Administration	YY0569-2005	18 July 2005	1 June 2006	American National Standards Institute NSF49-2002; Standardized Committee of Europe EN12469: 2000
Ministry of Construction	JG170-2005	25 March 2005	1 June 2005	

NSF49-2002 does not include these requirements, which were added to provide additional safety guarantees for the personnel working in Chinese biosafety facilities. In some instances, the test requirements (e.g., cleanliness) and product characteristics (e.g., noise level when operating) stated for BSCs in regulation JG170-2005 are also more rigorous than those stated in NSF49-2002 and EN12469: 2000.

Other main differences between Chinese, U.S., and European standards are first that while the European requirements only have a basic definition for Class II BSCs, the Chinese and U.S. regulations specify four types of Class II BSCs.[6] The European, Chinese, and U.S. standards all regulate in detail every testing method and the certification standards for the operational function of BSCs. As previously mentioned, the Chinese regulations, like the European ones, use the KI-Discus test to certify the level of protection from aerosol hazards that BSCs provide to laboratory workers. The American BSC regulation does not stipulate a permissible range for a reduced air velocity in Class II BSCs, but the Chinese and European regulations do.[7] The Chinese regulation divides reduced air velocity in two operational modes, namely, “even reduction” and

[6] The Chinese and U.S. Class II types are A1, A2, B1, and B2. Class II BSCs are defined mainly by the speed of the air current flowing into the front window of the cabinet, the air circulation in the cabinet, and the filter precautions for the exhaust.

[7] The range for reduced air velocity in YY0569 and EN12369 is 0.25-0.5m/s.

"non-uniform reduction." Finally, all of the standards identify numerous testing spots for operational tests.

Unlike the European and U.S. regulations, Chinese regulation YY0569 also clearly stipulates the design standard of cabinet body structure of class II BSCs (A2, B1, B2 types). The workspace of BSCs should be adopted on four sides (left, right, rear, and bottom sides) and in a double-deck structure. Consistent with the purpose of BSCs, which are designed to contain biological hazards, all of the air pressure gauges should be set to maintain negative flow or the BWC should be located in a negative pressure room with the appropriate ventilation system. The uncovered wall board of three sides of the Class II and Class III BSCs should be shaped into an integrated structure and sealed. Regulations require that BSCs in China undergo official examination and certification at least once annually.

To test the leakage of the BSC cabinet body, the Chinese regulation YY0569 adopts the U.S. and European standards of the pressure decay method, which uses a pressure gauge or pressure sensor system to show the pressure in the cabinet and can quantitatively measure the extent to which the cabinet body is airtight. Whereas the U.S. standard stipulates that manufacturers use the soap bubble method for their routine leakage test of all BSCs, EN12469 requires that leakage testing by done by an independent authentication laboratory.

While the three BSC standards discussed above have very much in common, the Chinese standards adopt the best from both the U.S. and the European standards and then improve on those models by including more accurate and rigorous methods for some key tests. Therefore, the Chinese testing standard for BSCs is one of the strictest in the world.

Biosafety Management of Medical Wastes

The management of medical wastes is linked to many activities, such as the collection, storage, handling, alteration, and transport of waste material. Many departments of the Chinese government, including the State Council, the Ministry of Health, and State Environmental Protection Agency have issued regulations and standards pertinent to the management of medical wastes. Table 4 lists these measures.

Table 4: Regulations Related to the Proper Management of Medical Wastes.

Title of the Regulation	Implementation Date
Management System for Hazardous Waste Transfers and Associated Documentation	1 October 1999
Requirements for the Discharge of Sewage from Medical Organizations	1 March 2002
Technical Standards for Disinfection	1 April 2003
Regulations on the Administration of Medical Wastes	16 June 2003
List of Medical Wastes	10 October 2003
Measures for Medical Waste Management at Medical and Health Institutions	15 October 2003
Regulation of Standards and Warnings for Special-Purpose Packaging or Containers for Medical Wastes	20 November 2003
Technical Guidelines for Waste Water Treatment at Hospitals	10 December 2003
Technical Specifications for Handling Medical Wastes	26 December 2003
Design Code for the Hospital Waste Water Treatment System	1 May 2004
Administrative Punishment Measures for Medical Waste Management	1 June 2004

The regulations in Table 4 create a comprehensive, concentrated, and strong system of management with responsibilities appropriately divided among participating organizations. These regulations cover activities from the generation to the treatment of medical wastes and strict safety controls are imposed throughout the entire process.

Among the detailed requirements for medical waste management are that the relevant administrative staff should receive training in the professional skills necessary to manage the proper disposition of medical wastes and should have effective hygiene safeguards in place. Medical wastes should be categorized and collected according to the waste categories in the "Classified Catalogue of Medical Wastes" and placed separately into the appropriate hazardous waste packaging containers. Any transportation of medical wastes from one location to another within the facility should be documented, and the special-purpose receptacle or barrel and the vehicle used to transport these wastes must meet relevant standards. The temporary storage area for medical wastes must be separated from the storage area for ordinary trash, posted with identification and warning signs, constructed to prevent exposure of the stored wastes to rain, rodents, or insects, and

have security to guard against theft of the medical wastes. The facilities that treat medical wastes have such features as a disinfection room, incinerators, a sewage disposal pool (e.g., septic tank, disinfection pool), and mud dehydration treatment facilities.

Another requirement of these standards is that medical organizations build waste water treatment facilities and institute regular monitoring of the generation of waste water. Several branches of local government are involved in the management of medical wastes. County, city, provincial, and national government authorities are responsible for building treatment facilities for medical wastes. The sanitation departments at these levels of governments are accountable for supervising measures to prevent disease during the process of collecting, handling, storage, and transport of medical wastes, as executed by sanitation departments. Finally, country, city, provincial, and national environmental protection agencies are in charge of the supervision and control of measures to prevent environmental pollution in the handling and disposition of medical wastes.

Noncompliance with the regulations governing medical waste management is to be penalized according to the "Administrative Punishments for Medical Waste Management." An organization that does not handle medical waste according to the regulations will be warned and ordered to come into regulatory compliance within a specific period of time. Should the organization not fix the problem within the time period identified, a fine of 1000 to 5000 Yuan (approximately $130 to $645) will be imposed. An institution that has not converted to the new, centralized system of hazardous waste management or that delivers medical waste to an organization that is not properly qualified to transport, store, or handle hazardous wastes will be directed to cease the illegal activities and to correct its noncompliance within a particular period of time. A fine of 50,000 Yuan (approximately $6,450) will be imposed if corrective action is not taken within the specified time period.

Reference Lists of Pathogenic Microorganisms

To enable the proper implementation of the regulations on biosafety management in laboratories, the Ministry of Health and the Ministry of Agriculture announced reference lists for human and animal pathogens on 13 May 2005 and 11 January 2006,

respectively.[8] The list of animal and human pathogenic microorganisms has 123 species and 380 species, respectively, as Table 5 shows. Based on a risk assessment of the pathogenic microorganisms, the regulations state that live pathogenic microorganisms (e.g., bacteria, viruses) in the Class I and Class II categories of risk should generally be restricted to BSL-3 or BSL-4 laboratories. Deactivated pathogens from these two risk categories can be worked with in BSL-2 laboratories. Activities with pathogenic microorganisms of the class III or IV risk are to be handled in BSL-2 or BSL-1 laboratories. These reference lists also factor into decisions about the appropriate biosecurity measures to be taken for the listed human and animal pathogens, as discussed later in this essay.

Table 5: China's Lists of Pathogens of Risk to Humans and to Animals.

List Category	Type of Pathogens	Category of Risk	Examples	Number of Pathogens in Risk Class
Animal Pathogens		Class I	Foot-and-mouth disease virus, highly pathogenic avian influenza virus, African horse sickness virus, Rinderpest virus, Peste des petits ruminants virus	10
		Class II	Classical swine fever virus, Newcastle disease virus, rabies virus, sheep smallpox virus, goat small pox virus, rabbit hemorrhagic disease virus, *Bacillus anthracis*	8
		Class III	Influenza virus with low pathogenicity, Pseudorabies virus , *Clostridium tetani, Clostridium chavuoei, Mycobacterium bovis*	107
		Class IV	Microorganisms with low infectivity, low pathogenicity and/or low toxicity not included in Class I, Class II and Class III	Not applicable

Table 5: China's Lists of Pathogens of Risk to Humans and to Animals, Continued.

[8] The Chinese government has not established a similar reference list for plant pathogens.

List Category	Type of Pathogens	Category of Risk	Examples	Number of Pathogens in Risk Class
Human Pathogens	Viruses	Class I	Alastrim virus, Eastern equine encephalitis virus, Ebola virus, Lassa fever virus, Monkeypox virus	29
		Class II	Foot-and-mouth disease virus, Herpesvirus saimiri, highly pathogenic avian influenza virus, Human immunodeficiency virus (HIV) type 1 and 2 virus, Japanese encephalitis virus	51
		Class III	Adenoviruses, Bunyavirus, Adeno-associated virus, Astrovirus, newly emerging viruses	74
		Class IV	Guinea pig herpes virus, Mouse leukemia virus, Mouse mammary tumor virus, Rat leukemia virus	6
	Prions	Class II	Transmissible spongiform encephalopathies (e.g., Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome)	5
		Class III	Scrapie	1
	Bacteria, actinomyces, mycoplasma, spirochaeta, etc.	Class II	*Bacillus anthracis, Brucella* spp, *Mycobacterium tuberculosis, Vibrio cholerae, Yersinia pestis*	10
		Class III	*Acinetobacter lwoffi, Acinetobacter baumannii*	145
	Fungi	Class II	*Coccidioides immitis, Histoplasm farcinimosum*	4
		Class III	*Absidia corymbifera*	55

Sources: "List of Animal Pathogenic Microorganisms" (Beijing: Ministry of Agriculture, 13 May 2005); "Directory of Pathogenic Microorganisms Transmissible Between Humans" (Beijing: Ministry of Health, 11 January 2006).

The Framework for Biosecurity in China

The system for biosecurity in China requires different approvals and increasingly rigorous security measures for the authorization to possess, to transfer, and to experiment with microorganisms, depending on the risk the microorganisms pose to human and

animal health and the environment. China's regulations for the proper storage of strain collections date back to 1980. The first of these regulations was the Ministry of Agriculture's "Methods on the Trial Management of the Preservation of Veterinary Microbial Strains," implemented on 25 November 1980 and revised on 1 July 2004. In the interim, the Ministry of Public Health "Methods on Management of Preservation of Medical-Microbiology Strains in China" on 23 March 1985 and the State Science and Technology Commission issued "Rules on Management of the Preservation of Microbial Strains in China" on 8 August 1986. These regulations all apply to human and animal microorganisms and are very detailed. They include: guidelines for the classification of strains, sample procedures for the collection of strains, the proper conditions for strain storage, the supply or sale of strains, the use of strains, and the acquisition, transfer, and exchange of strains with outside organizations. Under these regulations, the Ministry of Public Health and Ministry of Agriculture have appointed culture collection centers and laboratories to receive, preserve, and store microbial strains and samples. Thus, since 1980, any laboratories or culture collections across China not specifically designated to receive, preserve, and store pathogens but that had strains and samples of pathogens in their historical collections were required to destroy those strains or samples immediately or to deliver them to an authorized culture collection center.

The biosafety level of the laboratory and the reference lists created in 2005 and 2006 for the pathogens serve to establish two other levels for biosecurity in that organizations must meet certain additional criteria to work with any of the human and animal species on these lists, which are elaborated in Table 5. To qualify to receive and handle human and animal pathogens on these reference lists, an institution must be legally established and have a laboratory certified to engage in experimental activity with highly pathogenic microorganisms. The receiving institution must also obtain approval from the particular government offices responsible for experimental activity with highly pathogenic microorganisms, storage of microbial strains and samples, production of biological substances, or the other relevant activities. The third tier of the management and security system for highly pathogenic microorganisms is that culture collections and laboratories must receive an additional designation from the Ministry of Public Health and the Ministry of Agriculture to possess human and animal pathogens from Risk Groups 1 and

2. In addition, the laboratories must also obtain approval for the conduct of experimental research with individual highly pathogenic microorganisms from these risk groups or microorganisms suspected of falling into the Risk Groups 1 and 2 categories. Furthermore, the laboratories are to report to the public health or veterinary authorities above the provincial level for approval of shipment requests for pathogens from the reference lists. Three separate and additional approvals, in other words, are required to work with Risk Group 1 and 2 pathogens.

Any laboratory certified to work with highly pathogenic microorganisms should establish a sound security system for the laboratory and take measures to prevent the theft, robbery, loss, or release of any pathogenic microorganism. The level of security to be established is tied to the Risk Group of the reference list pathogens and to the biosafety level of the laboratory. For example, a BSL-4 laboratory working with Risk Group 1 microorganisms would have the tightest level of security.

Any facility applying to receive human and animal species from the reference lists has to have certain physical security and accountability measures in place to receive these strains. The personnel responsible for managing the organization's culture collection should make strict rules for the storage of and access to these highly pathogenic microorganisms. The facility should have a separate filing system to track all activities with these microorganisms, with a member of the staff specifically appointed to register when these strains and samples are originally received and each time thereafter they are accessed by facility personnel. All strains and samples from the reference list are to be kept in a special facility or in a separate, double-locked storage container. In addition, the areas where the listed pathogens are stored and worked with should have additional security measures, which might include video surveillance, a double fire-security door with a separate pass code or other entry system, and a guarded entrance where all who access the area can be observed. Finally, any individual handling a pathogen from Risk Group 1 or 2 is not allowed to work alone; at least two partners must be in the laboratory with them when an experiment involves these high-risk microorganisms.

Should theft or diversion of a pathogen from the reference lists occur, the institution must report it to local law enforcement and public health or veterinary authorities within two hours. The local authorities must in turn report the incident to the Ministry of Public

Health or the Ministry of Agriculture, as appropriate, within an hour. Penalties for the theft or diversion of pathogens, for the unauthorized possession or shipment of pathogens, and for experimenting with pathogens without the required approvals include the issuance of a warning, the loss of a job, and the loss of a license for the institution. Should the laws be broken and the consequences be deemed serious enough, the individual responsible would be investigated for criminal responsibility.

Standards for the Packaging and Authorized Transport of Microbial Strains and Pathogenic Microorganism Samples

To strengthen the biosafety management of pathogenic microorganisms and regulate the packaging and transport of microbial strains or samples of pathogenic microorganisms, the Ministry of Agriculture implemented on 24 May 2005 "Packaging Criterion on Transportation of Highly Pathogenic Animal Microbial Strains or Samples."[9] This criterion is based on the Dangerous Goods Regulations of the International Air Transport Association. This criterion establishes detailed regulations related to interior and exterior packaging materials, packaging precautions, and special requirement for the shipment of microbial strains or samples aboard civilian aircraft.

In addition, the Ministry of Public Health issued "Regulations on Transportation Management of Highly Pathogenic Microbial Strains or Samples of Microorganisms Contagious to Humans" on 1 February 2005 and implemented these regulations exactly a year later. These regulations establish firm requirements to qualify the shipping and receiving organizations for the transfer of human pathogens and strains and other details such as the formal application procedures for transfer, the procedures to verify the transfer, and the transportation requirements.

Shipment of any of the highly pathogenic animal or human strains or samples in Risk Groups 1 and 2 requires prior approval by the veterinary or public health authority at the provincial or national level. When transfers of highly pathogenic strains or samples from Risk Groups 1 and 2 occur, at least two trained escorts from the organization requesting the shipment must hand carry the vial(s) in appropriate packaging, never allowing the

[9] Storage, packaging, and transport activities are also accomplished in accordance with the relevant sections of the "Law on the Prevention and Treatment of Infectious Diseases," the "Regulation on the Biosafety Management of Pathogenic Microbiology Laboratories" and "Measures for the Examination and Approval of the Biosafety Administration of Pathogenic Microbiology Laboratories."

vial(s) to leave their sight. The containers and/or wrapping used to ship these highly pathogenic strains and samples must be in conformance with the packing standards for infectious substances issued by the International Civil Aviation Organization.[10] The commercial capacity to ship highly pathogenic substances in accordance with these standards is still being established in China.

Biosafety Oversight of Activities Involving Genetic Engineering

In December 1993, the State Science and Technology Commission released "Safety Administration Regulation on Genetic Engineering." This regulation was designed to govern all genetic engineering work in the People's Republic of China, including experimental research, intermediate experiments, the manufacture of commercial products, the release of genetically engineered microorganisms, and the use of genetically engineered products. The regulation defines "genetic engineering" as the direct introduction of alien DNA into a living organism using recombinant DNA technology (e.g., chemical methods, vector systems, physical methods). On a national level, the State Science and Technology Commission is responsible for the biosafety oversight of genetic engineering work and established the National Genetic Engineering Biosafety Council, which is responsible for the day-to-day supervision and coordination of activities related to the safe and responsible conduct of genetic engineering work.

The December 1993 regulation divided safety for genetic engineering work into four grades, but in some respects, this approach lacked operability or a plainly stated methodology to implement the four safety grades. To improve the oversight of genetic engineering activity, the Ministry of Agriculture issued "Safety Administration Implementation Regulation for Agricultural Biological Genetic Engineering" in July 1996. This second regulation was stronger because it clearly explained the security appraisals required of different genetic engineering bodies and their products, establishing the declaration and ratification system for agricultural bioengineering work.

Genetic engineering work is divided into four biosafety grades ranging from low to high risk according to the potential danger that the activity poses to human health and the

[10] Specifically, the requirement to be met is the Category A packing standard of "Infectious Substances: Technical Instructions for the Safe Transport of Dangerous Goods by Air," Guidance Doc. 9284 (Montreal: International Civil Aviation Organization: 2005/2006).

environment. Depending on the type of genetic engineering activity they are involved in, the responsible institution must evaluate different aspects of its project to enable the review and approval of the activity. For example, institutions performing genetic engineering experiments should carry out a comprehensive biosafety appraisal of the experiment encompassing the DNA donor, vector, host and genetic engineering body. The main contents of appraisal focus on the pathogenicity, carcinogenicity, drug resistance, and environment effects of the experiment. From this assessment, the appropriate level of biosafety procedures and physical containment controls can be authenticated. For experimental and intermediate level genetic engineering research, the evaluation would include such factors as whether the work will confer resistance to therapeutically useful antibiotics or antivirals, will enhance the virulence of a pathogen or render a non-pathogen virulent, will increase the transmissibility of a pathogen, and will change the natural host range of a pathogen.

Institutions conducting intermediate experimentation and industrial production that involves genetic engineering should identify the necessary physical containment barriers for the equipment and facilities used to culture, ferment, isolate, and purify genetically engineered material. Institutions engaging in the release of genetically engineered materials should evaluate genetic engineering body security, the purpose of release, the ecological conditions of the area where the material will be released, the methods of release and the monitoring of the release, control measures, and confirmation of the corresponding biosafety grade. The biosafety of the use of the genetically engineered products should be examined to confirm its possible influence on public health and the environment.

Review and approval for genetic engineering activities begins at the institution engaged in the genetic engineering activity. At the institutional level, scientists are required to register experiments for oversight if their experiment involves recombinant DNA activities; work with infectious agents; the use of human blood or other potentially infectious materials, such as unfixed human tissues, primary human cell lines, and certain bodily fluids; and/or work on animal and plant pathogens. For activities involving the higher grades of genetic engineering, the review and approval process moves to higher authorities, including the offices of the State Council and the National Genetic

Engineering Biosafety Council. Table 6 shows this progression, as well as circumstances where a record of the activity is registered, but approval of that organization is not required. After a project is reviewed and approved, the regulations require the institution engaged in the genetic engineering activity to submit progress reports and final reports on the outcome of the research or other activities to the authorizing organization(s).

Violations of the national regulations for oversight of genetic engineering work fall into three general categories: 1) conduct of genetic engineering work without prior review and approval; 2) use of devices, instruments, and laboratory facilities in discord with the regulations; and, 3) violation of the biosafety guidelines related to genetic engineering work. In the event of a violation, the genetic engineering activity must stop temporarily while an investigation is conducted. When someone breaks the regulations, their institution administers the following types of punishment, which escalate in their level of severity according to whether the violation is in the first, second, or third category of misbehavior. The punishments include a warning notice, dismissal from work, stopping of funds for the improper work, and confiscation of income gained through the illegal activity.

Chinese authorities have also addressed the biosafety management of genetic engineering involving human genetic resources. In June 1998, the Ministry of Science and Technology and The Ministry of Public Health also jointly issued "Interim Measures for the Administration of Human Genetic Resources" in June 1998.[11] The term "human genetic resources" refers to the genetic materials such as human organs, tissues, cells, blood specimens, preparations of any types or recombinant DNA constructs, which contain human genome, genes, or gene products as well as to the information related to such genetic materials. At the State Council, the administrative departments of science and technology and of public health share joint responsibility for the national administration of human genetic resources in China and jointly established the Human Genetic Resources Administration to carry out routine duties.

[11] Previously, the pertinent regulation on this subject was the Ministry of Agriculture's "Regulation on the Implementation of Safety Administration for Agricultural Biological Genetic Engineering," which was released in June 1996 and replaced in 2002 by the "Administrative Rules for the Safety Assessment of Agricultural GMOs."

Table 6: China's System for Review and Approval of Genetic Engineering Activities.

Genetic Engineering	Experimental Research	Intermediate Experiments	Industrial Production, Release of Genetically Engineered Material, Use of Genetically Engineered Products
Grade One (No Risk)	Administrative Director of Institute Approves	Administrative Director of Institute Approves	Appropriate Administrative Offices of State Council Approves + National Genetic Engineering Biosafety Council Records
Grade Two (Low Risk)	Administrative Director of Institute Approves	Administrative Director of Institute Approves + Appropriate Administrative Offices of State Council Approves	Appropriate Administrative Offices of State Council Approves + National Genetic Engineering Biosafety Council Records
Grade Three (Medium Risk)	Administrative Director of Institute Reviews + Appropriate Administrative Offices of State Council Approves	Administrative Director of Institute Examines + Appropriate Administrative Offices of State Council Approves + National Genetic Engineering Biosafety Council Records	Appropriate Administrative Offices of State Council Approves + National Genetic Engineering Biosafety Council Records
Grade Four (High Risk)	Appropriate Administrative Offices of State Council Examines + National Genetic Engineering Biosafety Council Approves	Appropriate Administrative Offices of State Council Examines + National Genetic Engineering Biosafety Council Approves	Appropriate Administrative Offices of State Council Examines + National Genetic Engineering Biosafety Council Approves

The Human Genetic Resources Administration of China performs the following activities: 1) drafting relevant rules and forms for the implementation of the rules,

disseminating approved rules to enable their entry into force, and ensuring enforcement of the rules through coordination and supervision; 2) managing the registration and administration of important pedigrees and genetic resources in the specified regions; 3) reviewing and examining international collaborative projects that involve human genetic resources in China; 4) reviewing and approving applications to export human genetic resources; and, 5) other duties related to the administration of human genetic resources in China.

If any Chinese institution or individual violates the rules by exporting the human genetic materials without authorization, whether by hand carrying, mailing, or otherwise transporting these materials, Chinese Customs authorities are to confiscate the materials. The punishment for the institution or individual responsible for the illegal export ranges from administrative sanctions to judicial prosecution, depending on the seriousness of the circumstances. Any individual or institution responsible for providing human genetic materials to foreign institutions or individuals without permission will be fined and the human genetic materials confiscated. For serious violations of this nature, the individual will be investigated for legal responsibility for his actions.

Biosafety Management of Activities Involving Genetically Modified Organisms

Building on the establishment of four grades of biosafety for genetic engineering activities, the State Council issued "Safety Administration Regulations for Agricultural GMOs" in May 2001, which extended biosafety management of agricultural genetically modified organisms (GMOs) to the production, processing, management, and import and export of GMO products. Since 2002, the Ministry of Agriculture announced four biosafety management standards related to the May 2001 regulations, specifically the identification, safety assessment, examination and processing approval, and safe import of agricultural GMOs. As indicated by the implementation of these laws and regulations, a standardized, legal approach has been taken with the biosafety management of agricultural GMOs in China. An additional thirty-two national and professional standards related to GMO testing supplement this framework.

Depending on the type of agricultural GMO activity, many biosafety management systems are being employed to oversee this work. These systems include differentiated

controls to identify, appraise, approve, and permit diverse agricultural GMO activities at various stages of research, testing, production, and sales activity. Chinese regulations state that agricultural GMO activities must be categorized into four grades of biosafety and into one of five stages of activity, namely experimental research, intermediate experimental research, environmental release, production testing, and application for biosafety certification. In each stage, a biosafety evaluation of the plant, animal, or microbiology GMO is completed, and approval is required and reported.

Individual biosafety certificates must be obtained for transgenic plant seeds, animal breeding stocks and birds, aquatic seedlings, and all other agricultural GMO products. Any organization that produces agricultural GMOs, including the production facility as whole and the individual production units therein, has to undergo a biosafety evaluation. If approved, the Ministry of Agriculture will issue the facility a business and a production license to make one or more certified agricultural GMOs. Manufacturing of agricultural GMO products can begin once the appropriate product certificates and facility licenses are secured. Local agricultural authorities at the provincial level of government are also responsible for assessing the regulatory compliance of manufacturing facilities, including individual production units that process raw materials (e.g., genetically modified plants, animals, crops), including activated GMOs that have a biological activity such as replication. Such manufacturing facilities must also be licensed before they can engage in processing agricultural GMOs.

All GMO products sold in China must be correctly identified, and an agricultural GMO catalogue has been established for that purpose. This catalogue lists, for example, agricultural GMOs for soybean seed, soybeans, soybean flour, soybean oil, soybean meal, maize seed, maize, maize oil, maize flour, rapeseed, rapeseed oil, rapeseed meal, cotton seed, tomato seed, delicious tomatoes, and tomato ketchup, all of which have received Chinese government approval. Any agricultural GMOs imported into China must be researched, tested, produced, and processed according to applicable Chinese standards to protect China’s food and environmental security.

Nationwide, the Ministry of Agriculture is responsible for the supervision of the biosafety of agricultural GMO activities. The ministry’s Biosafety Management Office for Agricultural GMOs has the lead in this regard. However, given the wide scope of

scientific and commercial activity involved in agricultural GMOs, an interdepartmental conference that draws specialists from the departments of agriculture, science and technology, hygiene, commerce, environmental protection, and inspection and quarantine is charged with studying and coordinating important biosafety management issues related to agricultural GMOs. To provide additional technical support, an advisory system for biosafety evaluation has been established. The national biosafety councils for agricultural GMOs consist of many experts engaged in distinct areas of agricultural GMO activity, such as research, production, processing, inspection and quarantine, hygiene, and environmental protection. These councils are responsible for the biosafety appraisal of GMOs. In addition, three organizations have been created to detect agricultural GMOs for environmental security, food security, and product inspection. The purpose of this detection activity is to demonstrate that agricultural GMOs are not present in food or other products that are not supposed to contain agricultural GMOs and that certified GMOs have not drifted to fields adjacent to the areas growing certified agricultural GMO crops. With this comprehensive approach, China's system of biosafety standards and management for agricultural GMOs is being progressively improved.

Concluding Observations

Governments and scientists around the world care about and pay attention to biosafety because of its importance to the both survival and enrichment of human society. In recent years, China has made rapid progress in the improvement of its biosafety standards and the implementation of those standards in many areas. These improvements encompass the areas of laboratory biosafety procedures and management, biosafety construction and equipment requirements, biosecurity of transfers for pathogens that are highly infectious to humans and to animals, oversight of genetic engineering, and biosafety appraisal and management of agricultural GMO activities.

Given the rapid developments taking place in biotechnology and the severe threat of global epidemics that could arise from outbreaks of infectious diseases, however, additional steps to improve biosafety should be taken in China and around the globe. Two important measures, for example, should be taken to enhance biosafety. A continuous program to improve the biosafety training of scientists and technicians who

work with highly pathogenic microorganisms should be instituted. Also, scientists, technicians, and bureaucratic specialists from around the world should be encouraged to participate in exchanges and cooperation on matters of biosecurity. To strengthen this international scientific, technical, and managerial cooperation on biosafety, governments should provide support for such exchanges. The extent to which biosafety is rigorously implemented in China as well as in all other countries will significantly influence the well-being of society.

Chinese Biosafety Laws and Regulations, Including Matters of Biosecurity and Oversight of Genetic Engineering Activities