FACT SHEET

Large-Scale Use of Biological Materials

This fact sheet provides guidance on the large-scale use of biological materials. "Large-scale use" is defined as greater than 10 liters of biological material (e.g., cultures, solutions) in one container. Large-scale containers include fermenters, bioreactors, carboys, or specialty equipment such as "tubes." The use of large-scale materials in research and teaching is governed by the National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) and by the Centers for Disease Control (CDC) guidance document Biosafety in Microbiological and Biomedical Laboratories (BMBL), Appendix M. At the University of Utah, large-scale use must be reviewed and approved by the Institutional Biosafety Committee (IBC).

University of Utah Oversight

The NIH Guidelines and the BMBL detail procedures for the containment and safe conduct of various forms of research, including work with large volumes of biological materials. All researchers at the University of Utah must comply with the NIH Guidelines and BMBL even if the NIH does not fund their individual projects. In addition, a permit from the USDA/APHIS is required for the importation, interstate movement or environmental release of genetically modified organisms.

At the University of Utah, the IBC oversees all research, teaching, and production of biological materials in volumes greater than 10 liters in one vessel. The IBC reviews and approves large-scale use for compliance with the NIH Guidelines, University of Utah policies, and best laboratory practices. The University of Utah IBC reviews the handling of all large-scale research, even that which may be exempt from the NIH Guidelines, so that the University of Utah, acting through the IBC, can ensure that all recombinant DNA research is appropriately reviewed and classified.

Principal Investigators (PIs) must submit a registration to the IBC before beginning work with biological volumes greater than 10 liters. The IBC registration must be completed in BioRAFT. EHS Biosafety personnel will inspect the equipment and set-up before operation begins. As part of the IBC registration, the PI must provide the following standard operating procedures (SOPs):

- harvesting
- inoculation
- large spills
- medical evaluation and treatment
- normal operation
- secondary containment
- small spills
- transporting between locations
- validating destruction (including all mathematical calculations for disinfection); and
- waste disposal

University of Utah PIs are responsible for compliance with the NIH Guidelines while conducting research or production with large-scale cultures and solutions. Additionally, the PI must notify the IBC before modifying research already approved and promptly report any problems with containment procedures, violations of the NIH Guidelines, or any research-related accidents and illnesses.

Large-Scale Use under the NIH Guidelines

Large-scale experiments are governed by NIH Guidelines Section III-D-6, Experiments Involving More than 10 Liters of Culture. This section specifies that the appropriate containment for large-scale work be decided by the IBC and that Appendix K, Physical Containment for Large Scale Uses of Organisms Containing Recombinant or Synthetic Nucleic Acid Molecules, should be used where appropriate. Appendix K discusses how to select the appropriate physical containment level. It describes work practices and facility requirements for Good Large Scale Practice, Biosafety Level 1–Large Scale, Biosafety Level 2–Large Scale, and Biosafety Level 3–Large Scale. Finally, it has definitions, footnotes, and a table comparing the different levels of large-scale practice.

Selection of Physical Containment Levels

Good Large Scale Practice (GLSP) is for work involving viable, non-pathogenic and non-toxigenic strains derived from host organisms that have a history of safe large-scale use and are free of adventitious agents. GLSP is recommended for organisms such as those in NIH Guidelines Appendix C, which have built-in environmental limitations. The organisms that may be used at GLSP are described in Appendix K-VII-G and following:

The host organism should:	• be non-pathogenic and non-toxigenic; • not contain adventitious agents; and • have an extended history of safe large-scale use or have built-in environmental limitations that limit survival without adverse consequences in the environment.
The recombinant engineered organism should be:	• non-pathogenic and non-toxigenic; • as safe in the large-scale setting as the host organism; and • without adverse consequences in the environment.
The vector/insert should be:	• well characterized and free from known harmful sequences; • limited in size as much as possible to the DNA required to perform the intended function; and • poorly mobilizable;
Also, the vector/insert should:	• not increase the stability of the construct in the environment unless that is a requirement of the intended function; and • not transfer any drug resistance markers to microorganisms not known to acquire them naturally if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture.

Biosafety Level 1-Large Scale (BSL1-LS) is for biological materials that require BSL-1 containment at the laboratory scale and that do not qualify for GLSP. BSL2–Large Scale (BSL2-LS) is for large-scale use of organisms that require BSL2 containment at the laboratory scale and BSL3–Large Scale (BSL3-LS) is for large-scale use of organisms that require BSL3 containment at the laboratory scale. BSL2-LS and BSL3-LS are not discussed in this document.

Containment and Work Practices for GLSP and BL1-LS (Appendices K-II and K-III of the NIH Guidelines and Table) GLSP and BSL1-LS have some similar requirements for containment and work including:

- standard practices for personnel safety;
- training and standard operating procedures;
- personal protective equipment according to risk;
- appropriate facilities, equipment, and work practices to safeguard health;
- reporting accidents and incidents;
- medical treatment as appropriate;
- inactivation of waste; and
- emergency plans for handling a large loss of biological material.

However, there are further requirements for BSL1-LS that are not needed for GLSP (see Appendix K-III of the NIH Guidelines for details). These are primarily about preventing aerosol releases and include:

- a closed system or other primary containment that separates viable organisms from external environment;• controlling aerosols by engineering to minimize release during sampling, addition of material, transfer of cultivated cells, and removal of material, products, and effluent from the system;
- treating exhaust gases to minimize release;
- inactivating the material before removal from the system (unless it is the final product); and
- sterilizing the closed system by a validated procedure before it is opened.

In order to be classified as GLSP, documentation must be submitted to the IBC, which demonstrates that the organism has an extensive history of safe large-scale use or that there are built-in characteristics, which limit its survival in the environment. Contact EHS Biosafety to discuss proper classification, containment levels, and operating requirements.

Environmental Release

A release, leak, spill, or other loss of containment of a large-scale material is a serious issue. Loss of a culture or biological solution outside of containment, for instance onto the ground, floor or into a sewer, must be reported to EHS Biosafety. There are federal and state reporting requirements for such incidents.