

## **Impact of U.S. Export Regulations on the Timely Response to an Influenza Pandemic**

**Betty Lee, Ph.D.  
Department of Commerce  
Bureau of Industry and Security  
Office of Non-Proliferation and Treaty Compliance  
Chemical and Biological Controls Division  
Washington, DC**

### **Introduction**

In the event of a pandemic, such as the H1N1 influenza outbreak in 2009, worldwide cooperation in vaccine production, exchange of virus samples among countries affected, and also regulatory approvals are essential to combat the widespread disease. The Center for Disease Control (CDC) in Atlanta, Georgia, coordinates public health information for the nation and keeps the public informed about outbreaks, vaccination, treatment and availability of vaccines. Between April and December 2009, the CDC estimated that an average of 55 million people was infected with H1N1 virus.

The World Health Organization (WHO) is responsible for disseminating health information on global health matters, shaping health research agenda, setting standards, providing technical support, and monitoring the health situation worldwide. One of the functions of the WHO is to promote international health security from outbreaks of emerging infectious diseases. This is a shared responsibility among nations. When an influenza pandemic occurs, are there U.S. regulations that govern the export of vaccines to certain countries?

There are U.S. regulations that govern the transfer of controlled dual-use technology, microorganisms, and equipment to countries that may impact the exchange of information and cooperation between countries. The Department of Commerce, Bureau of Industry and Security (BIS) has the jurisdiction of overseeing dual-use exports that have an impact on the national security of the nation. BIS is responsible for implementing and enforcing the Export Administration Regulations (EAR), which regulates the export and re-export of most dual-use items to advance the national security, foreign policy and economic interests of the United States of America.

## Multilateral Regimes

The EAR gives BIS the jurisdiction over dual-use technology, biological, and chemical processing equipment that also has potential for biological and chemical warfare. The United States is a member of the Australia Group (AG), an informal group of countries that seeks to ensure that exports do not contribute to the development of biological and chemical weapons. This is a multilateral regime, and the membership has grown from 15 members in 1985 to 40 members plus the European Commission.

The main objective of the AG is to use licenses to ensure that chemicals, biological agents, dual-use chemical and biological processing equipment do not contribute to the spread of chemical and biological weapons (CBW). The AG maintains a control list of dual-use biological equipment, related technology and software (AG, 2007). The control lists developed by the AG include equipment and technologies that can be used in the manufacturing or disposal of biological and chemical weapons.

Member countries of the AG are parties to the Chemical Weapons Conventions and the Biological Weapons Convention (BWC) (AG, 2010). The scope of the export controls encompasses emerging threats and challenges posed by these threats. The AG's activities are limited to non-proliferation measures, and do not help the commercial development of industries in member countries or obstruct the legitimate economic development in other countries.

## Commerce Control List (CCL) and Biological Select Agent and Toxins List (BSAT)

Similarly, BIS maintains a list called the Commerce Control List (CCL), which also reflects the AG list. The CCL is found in Supplement No. 1 to part 774 of the EAR (EAR, 2010). Dual-use biological agents, toxins and related technology are listed in Category 1 of the CCL, while biological, chemical processing equipment and related technology are listed in Category 2 of the CCL. The Commerce Country Chart is found in Supplement No. 1 to part 738, which explains the licensing requirements based on destination and reasons for control.

Biological agents and toxins on the CCL also include similar microorganisms and toxins of the Biological Select Agent and Toxins (BSAT) list, maintained by the Department of Health and Human Services (DHHS) and the U.S. Department of Agriculture (USDA) (BSAT, 2010). In addition, genetic elements, such as modified DNA, pathogenic sequences of controlled microorganisms and toxins are also controlled on the CCL. The CCL is updated when there are changes to the AG list or the BSAT list. The updates are posted on the Federal Register and on the online version of the EAR (Orr and Lee, 2009).

In addition, there are other lists on the BIS' website, which any researcher or pharmaceutical company needs to check before applying for a license to export controlled microorganisms, DNA, technology, or biological processing equipment (BIS, 2010). Table 1 shows a representative sample of lists maintained by Commerce and DHHS. The State Department and the Department of Treasury also maintain lists that would need to be checked before an export transaction happens.

<b>Lists</b>	<b>Description</b>
CCL	Microorganisms, toxins, genetic elements, biological & chemical processing equipment
BSAT	Pathogenic microorganisms for human, animal, and plant diseases
Entity	Businesses, research institutions, government and private organizations, individuals, and other types of legal persons that are subject to specific license requirements for the export, re-export, and/or transfer (in-country) of specified items
Unverified	Foreign persons who had applied for export licenses whereby BIS could not conduct a pre-license check (PLC) or a post-shipment verification (PSV) for reasons outside of the U.S. government's control
Denied Persons	Persons that have been denied a license in the past

**Table1. Examples of Lists and Their Descriptions**

## **International Research Collaborations**

What are the guidelines that govern the exchange of a highly infectious avian H51N virus to a collaborating researcher in another country? In this scenario, the U.S. government requires an export license for this virus to every country because it is listed on the CCL. Therefore, it is the responsibility of the researcher or biotechnology company to apply to the Department of Commerce for an export license at least 45 days before the transfer of the virus. It is advisable to apply for a license early, once it is ascertained that a license is required for the transaction.

What should a researcher be aware of when the need arises for a genetically modified, highly pathogenic avian influenza virus or a genetically modified, genomic DNA sequence to be donated to a foreign researcher for the purpose of developing a diagnostic test or manufacturing a vaccine? Sometimes, the CDC has ongoing research collaboration with an institute in another country that has an outbreak of an infectious disease such as avian influenza.

In this case, CDC will need a license to export the avian influenza virus or genomic DNA of the virus because both of these items are controlled on the CCL. As most licenses are valid for two years, researchers may export the research material up to the maximum quantity approved on the license in several shipments. In order to maintain the ongoing collaboration, a new license will be needed before the expiration of a current license. This is important to ensure there is no interruption in the exchange of material between the two countries.

Vaccines against any of the controlled microorganisms are classified as 1C991 in the CCL. Export licenses of vaccines are not required for most countries, except the sanctioned or embargoed countries, which include Iran, North Korea, Sudan, Cuba and Syria.

For example, if there is an outbreak of Dengue hemorrhagic fever in a region of the globe that is endemic to the disease, a sample of the Dengue virus isolate may be needed to develop a vaccine in that country. A researcher in the U.S. will need to apply for an export license to donate the isolate or viral DNA to a collaborator in that country. If the researcher exports the controlled

item without a license, then he or she will be in violation of the EAR and may be subject to a civil or criminal prosecution.

## **Deemed Export**

The term “deemed export” causes a lot of confusion when research laboratories have many foreign students or researchers. It refers to any foreign national who requires a deemed export license because they are working on technology controlled in the CCL (Orr and Lee, 2009). People who are exempt from a deemed export license are green card holders or permanent residents, those with U.S. citizenship, or "protected persons" under 8 USC 1324b(a)(3). However, if a foreign national is doing ‘fundamental’ research, as defined by the EAR Section 734.8 (EAR 2010), then he or she does not require a license. A person doing non-fundamental research involving the growth or genetic manipulation of a listed microorganism would require a deemed export license.

If the foreign researcher is working in the U.S. on controlled technology, then a deemed export license is required for the individual. Any transfer of technology in the form of electronic communication such as emails, oral and/or attendance at international conferences are considered as deemed exports.

## **Biological Manufacturing Equipment for Production of Vaccines and Therapeutics**

Most biological processing equipment, such as fermenters, cross-flow filtration devices, Class III biological safety cabinets, freeze-drying equipment, aerosol testing chambers, and so forth, are listed as controlled dual-use items on the CCL. Complete containment facilities at the biosafety level (BSL) 3 or 4 are also controlled. Pharmaceutical and biotechnology industries that manufacture vaccines and therapeutics will need some of this equipment for their manufacturing processes. Licenses of these items are required to most countries.

If a foreign biotechnology company has an agreement to manufacture a vaccine, it may need a continuing supply of cross flow-filtration modules or devices for the production of the vaccine. These filters are essential in purifying biological drugs and vaccines for use in humans and animals. The supplies are needed on an ongoing basis for continual production of the vaccine. In such cases, before the supplies are exhausted, new licenses have to be applied in order to prevent vaccine shortage.

If there is a necessity to increase production of a biological therapeutic, several large fermenters (or bioreactors) would be needed for growing mammalian cells or bacterial cultures. Biotechnology companies will need export licenses to acquire such essential equipment.

## **H1N1 Pandemic**

The World Health Organization has recently declared the spread of H1N1 virus as a global pandemic. It has been 41 years since the world experienced a pandemic. Does the transfer of H1N1 virus stock for vaccine production require an export license under the current regulations?

Under the current regulations, the H1N1 virus is not on the CCL and, therefore, no license is required for its export to other countries. Researchers and government institutes may transfer these virus isolates to collaborators overseas for development of vaccines against the virus. As the H1N1 virus is not on the CCL, then any viral DNA or genetic element from this particular virus can be transferred to most countries without a license. The exceptions to this rule are the sanctioned countries. Exports to these countries, even if there is an international research collaboration sponsored by the WHO or CDC, will require licenses for exports.

## **Sanctioned Countries**

Medicines, medical devices, and equipment are subject to the EAR and are classified as EAR99. In general, licenses are not required for exports to most countries. However, licenses are required for exports to Iran, North Korea, Cuba, Sudan and Syria. These licenses are reviewed on a case-by-case basis.

Are there any restrictions to the export of H1N1 vaccines to sanctioned countries, such as Iran, North Korea, Cuba, Sudan or Syria? As the H1N1 virus is not controlled, then the H1N1 vaccine would be considered EAR99. This EAR99 designation means that the item is subject to the EAR but it does not necessarily mean that a license is required for export to most countries. However, in the case of the sanctioned countries, they will require licenses.

In pandemics, time is of the essence to combat the spread of the disease. Therefore, there is an urgency to transfer effective therapeutic treatment to affected countries to reduce the impact of the disease. How does the federal government balance need for humanitarian aid and biosecurity?

In cases when there is an immediate need for vaccines to affected countries, the interagency application review process can be expedited to reduce the number of days for approval of these licenses. Nevertheless, the application process needs to be started early to permit time for the interagency review.

## **Conclusion**

In summary, U.S. export regulations have a significant impact in the collaboration of researchers and pharmaceutical companies for the exchange of technology, vaccines, and biological samples when there is the emergence of a pandemic. These laws have to be followed and adhered to despite the urgency of the situation. The approval of these licenses can be expedited on a case-by-case basis. Multilateral regimes, such as the AG, have similar export controls, which are implemented in the member countries to deter proliferation of biological and chemical weapons. The U.S. government has to balance the humanitarian needs and biosecurity to protect its citizens.

## **Bibliography**

Australia Group (AG) 2010 (retrieved February 7, 2010)  
(<http://www.australiagroup.net/en/index.html>).

Bureau of Industry and Security (BIS) 2010 website (retrieved February 7, 2010)  
(<http://www.bis.doc.gov>).

Export Administration Regulations (EAR), 15 CFR chapter VII, subchapter C (retrieved February 7, 2010) (<http://www.access.gpo.gov/bis/ear/pdf/738.pdf>).

Biological Select Agent and Toxins (BSAT) List, 7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73 (retrieved February 7, 2010)  
(<http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20List.html>).

Orr, K. and B. Lee. 2009. "Demystifying Department of Commerce Export Controls for the Biosafety Professional." *Applied Biosafety*, Vol 14, No. 2 (www.absa.org).