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INTERNATIONAL BIOLOGICAL and CHEMICAL THREAT REDUCTION

Biosecurity for Vaccine Producers Module 1: Dual Use Equipment of Concern

dcvmn
Developing Countries Vaccine Manufacturers Network

CBEP

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Action Plan

By the end of this lesson, I would like to:					
KNOW		FEEL		BE ABLE TO DO	

Your learning doesn't stop with this lesson. Use this space to think about what else you need to do or learn to put the information from this lesson into practice.

What more do I need to know or do?	How will I acquire the knowledge or skills?	How will I know that I've succeeded?	How will I use this new learning in my job?

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Key Messages

- Many types of vaccine production equipment are considered dual-use equipment.
- The only difference between a vaccine and a bioterror agent – is the final inactivation step
- Vaccine producers have a responsibility to control assets that might have interest for adversaries
- The Dual Use equipment should be handled in a way that proliferation does not occur.

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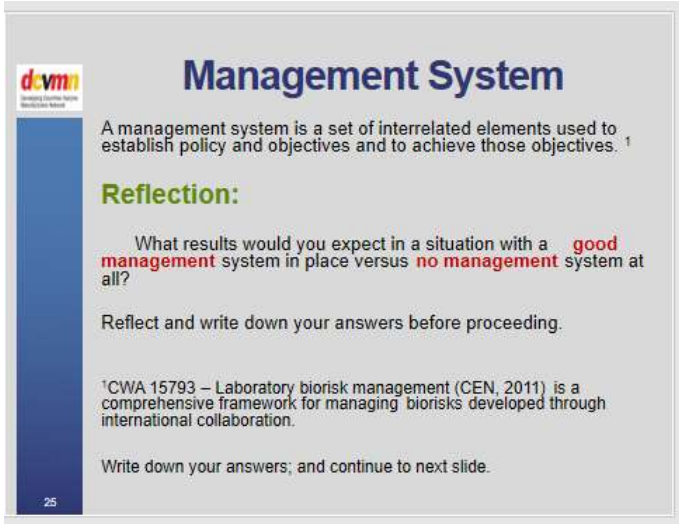
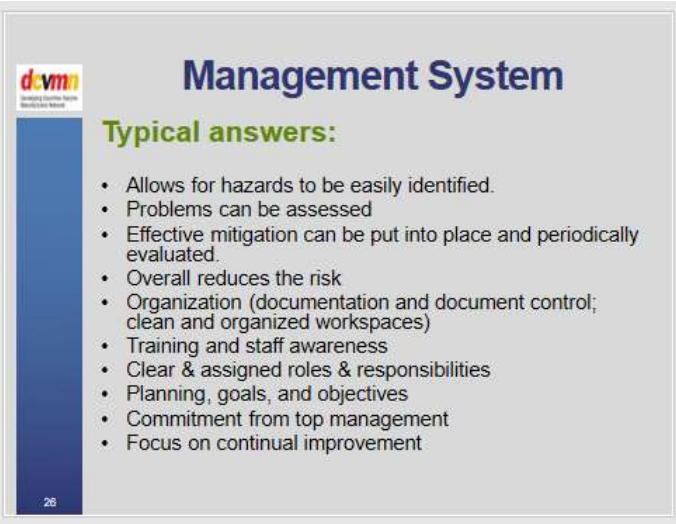
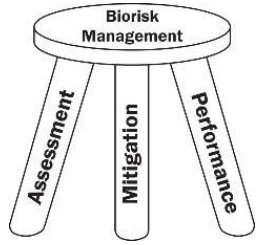
Why "Reflection" ?

During this lecture, we will ask you to consider some questions and then write down your answers before you advance to the next slide. In our training experience, this type of participation makes the training more relevant and useful to your situation. We encourage you to take the time to think about these questions and participate in the lecture.





Biorisk Management = Assessment, Mitigation, Performance



Assessment

- Process of identifying the hazards and evaluating the risks associated with biological agents and toxins, taking into account the adequacy of any existing controls, and deciding whether or not the risks are acceptable

Mitigation

- Actions and control measures that are put into place to reduce or eliminate the risks associated with biological agents and toxins

Performance

- Recording & evaluation of measurements to provide evidence that an organization is reliably and continuously conducting accurate biorisk assessment and implementing biorisk assessments and implementing biorisk mitigation strategies that effectively reduce or eliminate identified biorisks to an acceptable degree.

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Production Equipment

Reflection:

On a piece of paper list all the types of equipment that you can think of being used in your production facility for production of a vaccine.

- Upstream
- Downstream

Write down your answers and continue to the next slide.

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Production Equipment

Typical answers:

Fermentor
Bioreactor
Centrifuge
Freeze dryer
Purification column
Filter systems
……
……..
……..
……..
…..

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Why are We Producing Vaccines?

Reflection:

On a piece of paper list all the reasons for your facility to exist:

Write down your answers and continue to the next slide.

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Why are We Producing Vaccines?

Typical answers:

- Save lives
- Enhance quality of life for the population
- Save money for the health system
- And of course - earn money as a company

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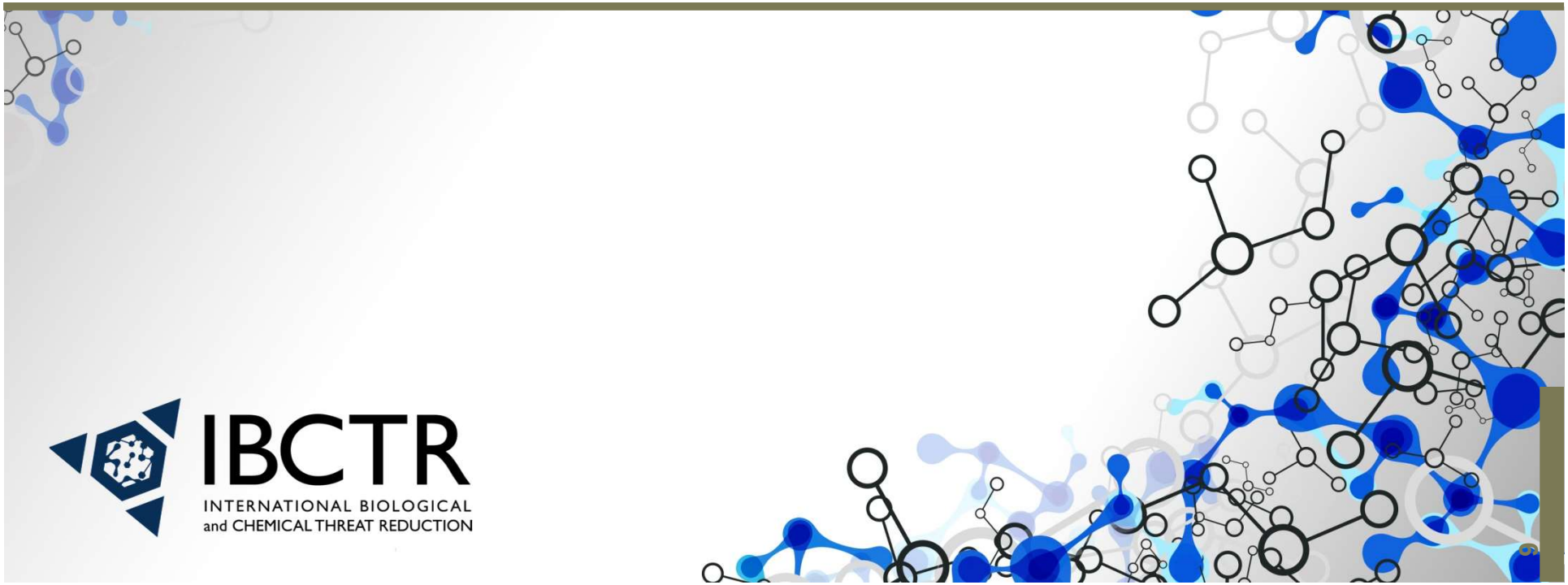
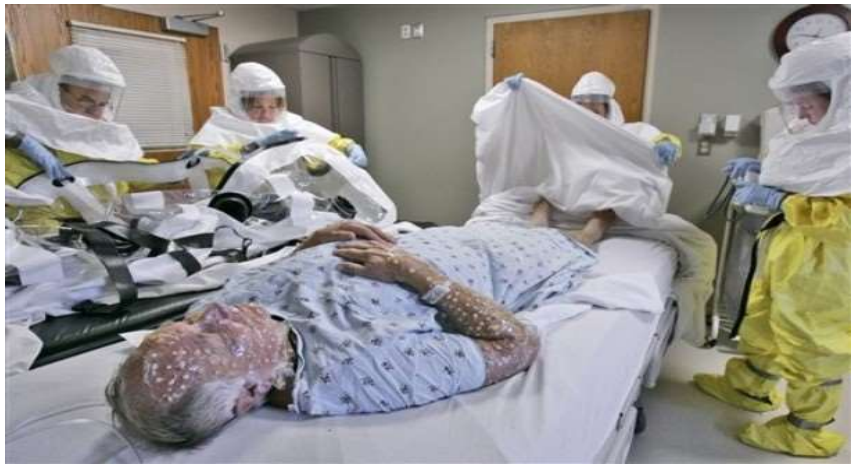
INTRODUCTION



Have You Ever Thought About

That the only difference between a vaccine and a biological weapon:

…. is the choice of agent and final inactivation step



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Biosecurity in Vaccine Productions

There is a rising need for vaccine manufacturers to understand and implement biosecurity and biosafety measures at their facilities

- The **biological materials** have a potential for infection, ……. that is why we are producing the vaccines to protect the hosts against infectious diseases
- The **equipment** utilized in the productions can be used for other biological processes as well
- And the specialized **technical knowledge** are all attractive targets for terrorist groups with a stated intent to conduct biological attacks

In November 2015, ISIS executed Head of Physics Department for refusing to develop bioweapons in Mosul. Mamoun, A. (2015). Source: *Iraqi News*
https://www.files.ethz.ch/isn/146155/Country%20Reports%20on%20Terrorism%202009_141114.pdf

Single Use Equipment

Single-use equipment is becoming more and more the standard in the production process of biological and pharmaceutical facilities.

- It is easy to operate
- Acceptable price
- Easily available

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Awareness of the Risk

The dual use aspect of the production equipment paired with single-use equipment availability becomes an even more volatile mixture.

Many manufacturers are unaware of the risks associated with dual-use equipment, large-scale production knowledge and techniques.

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Vaccine Company Drivers

Unfortunately, most vaccine producers are unaware of how big and attractive a target their employees and technology actually are for people that want to do harm

Most vaccine producers have difficulty envisioning that anyone would want to do harm and most do not have any concerns regarding what happens with old discarded stainless steel production equipment or with unused single use equipment.

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Consequences

Reflection:

What could be some of the consequences for the company if your facility was targeted by adversaries and the following were targeted?

- Seed agents/cell lines stored in cryo were stolen
- Production equipment sitting in warehouse were stolen
- Production equipment in use were stolen
- Bulk product from a stainless steel fermentor were tapped and stolen
- Bulk product in a single use system on wheels were rolled out of the production
- Final product awaiting final release were tampered with

Write down your answers and continue to the next slide.

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Agents / Seed / Cell lines

Typical answers:

- *Seed agents/cell lines stored in cryo container were stolen*
  - The whole basis and business model of the facility may be at risk – no master seed lots to make new batches of vaccines
  - Agents can be used by competitors for acquiring a similar market somewhere else
  - Agents can be used directly on a vulnerable human or animal community

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Production Equipment

Typical answers:

- *Production equipment sitting in a warehouse were stolen*
  - Adversaries can acquire export controlled equipment by this way, and the UNSCR 1540/BWTC has been circumvented
  - New batches might be delayed, impacting vaccination schedules for the costumers

- *Production equipment in use were stolen*
  - Batch is lost, impact on delivery time, vaccination schedule, revenue, company credibility

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Product

Typical answers:

- *Bulk product from a stainless steel fermentor were tapped and stolen*
  - Contamination/compromise of the rest of the batch by non-aseptic sampling technique
  - Non-inactivated product could be used as seed material for other large scale batches somewhere else

- *Bulk product in a single use system on wheels were rolled out of the production*
  - Final product for market would not be available, causing potential stop in vaccination campaigns, loss of revenue and credibility
  - Non-inactivated product could be used as seed material for other large scale batches

- *Final vaccine product awaiting final release was tampered with*
  - Product will have to be discarded
  - Product can not be released for sale, as there might be spiked contaminants in the product that the pharmacopeias do not anticipate. We do not know what to look for

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Vaccine Company Drivers

Conclusion

- Should a vaccine producer be targeted by people with malicious intent, the final consequences can be dire and severe.
    - *The producer will be the source associated with the outbreak or the attack.*
    - *It can have dire business consequences for the future of the facility.*
    - *Outbreaks and pandemics can be envisioned as a plausible outcome, and history has shown that this type of bio-terrorism has happened in the past.*

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Vaccine Company Drivers

The individual vaccine companies do not have any obvious up-front drivers for adding on assumingly tedious Bio Risk Management (BRM) procedures and policies (that are not mandatory by law), as these do not clearly give any immediate revenue and benefits for the facility.

Certifying Vaccine authorities do not see it as their mandate to enforce BioSafety and Security (BS&S) procedures, as these entities primarily focus on *protecting the product and the end user* and not to the same degree protecting the employees, the environment and the community.

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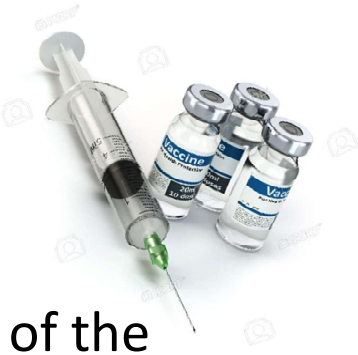
Staff Safety and Environment



Normally **there will be vaccines available** for the staff for any of the infectious agents used in the specific facility.

- Therefore, the most urgent BRM driver, keeping the employees healthy and protected from acquiring a laboratory infection (LAI) is not of immediate concern for the management***, because exposure will not necessarily result in disease*.**

That leaves the national environmental regulation as the **only** driver to introduce a comprehensive biosafety engagement strategy, for preventing release.

Unless vaccine companies respond to the threat and take own actions to secure their material with dual-use potential

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The Biological Weapons Convention

(BWC)

The Biological and Toxin Weapons Convention (BTWC) is an international treaty that went into effect in 1975. It bans the use of biological weapons and prohibits all development, production, acquisition, stockpiling or transfer of such weapons.

It was the first multilateral disarmament treaty banning an entire category of weapons, as States Parties to the BWC undertook "never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:

1. Microbial, other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes;

2. Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict."

The Convention effectively prohibits the development, production, acquisition, transfer, retention, stockpiling and use of biological and toxin weapons.

https://www.un.org/disarmament/wmd/bio/

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UNSCR 1540

All members of the UN, close to 200 sovereign states, have unanimously adopted the United Nations Security Council Resolution 1540 of 28 April 2004.

The resolution requires the UN Member States to take legislative and other national measures to prohibit and prevent the proliferation of nuclear, chemical and biological weapons to non-state actors, particularly terrorists and to report on implementation to the United Nations 1540 Committee.

It focuses on acquiring, manufacturing, possessing, transporting, transferring, or using nuclear, chemical, or biological weapons

United Nations Security Council Resolution 1540 (2004):
http://www.un.org/en/sc/1540/

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Council regulation (EC) no 428/2009

Furthermore, there are implementation documents, such as council regulation (EC) no 428/2009 of May 2009 that focuses on how to set up a community regime for the control of exports, transfer, brokering and transit of dual-use items. It is a comprehensive document that **lists both agents and related materials**. Related materials can be equipment as fermentors, centrifuges, spray systems, filter systems, lyophilizers and knowledge/information.

- Council regulation (EC) no 428/2009 of May 2009:
  http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:134:0001:0269:en:PDF
  page 69-86 list of agents, page 104–109 lists of equipment of concern.

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Implementation of Biosecurity Measures

A few countries have implemented an actual biosecurity law as a direct result of the UNSCR 1540.

- They have issued both **legislation and administrative procedures** for handling agents of concern.
- As time goes by, more and more countries are revising their legislation with regard to dangerous agents.

Very few countries have a biosecurity law that covers both agents and related materials.

For the vaccine industry, it is especially the related materials (equipment) and knowledge that are of biggest concern, as they relate to the very specialized skillset required to propagate small volumes of material into very large volumes.

As long as a real biosecurity law is not implemented and enforced in a country, it is difficult to envision that the vaccine producers will, on their own, change their priorities and behavior over-night.

HOWEVER; In the absence of legal constraints, ethical conduct is still important as a societal benefit.

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Dual-Use Technology

Reflection

Take the list of vaccine production equipment you created earlier in this course and compare it to the official list of dual-use equipment in the document

(use the link provided earlier for the *Council regulation (EC) no 428/2009 of May 2009*: or use the PDF handout that is listed for this course for an easier overview) .

Dual use equipment and technology of concern, from page 104 – 109, Council regulation (EC) no 428/2009 of May 2009	
Vaccine production equipment	
	Fermenters of less than 20 litre capacity with special emphasis on aggregate orders or designs for use in combined systems.
	Fermentors capable of cultivation of pathogenic microorganisms, viruses or capable of toxin production, without the propagation of aerosols, and having a total capacity of min 20 l. (Includes [single-use or stainless steel] bioreactors, chemostats and continous flow systems)
	Spray drying equipment capable of drying toxins or pathogenic microorganisms having all of the following characteristics: a water evaporation capacity of ≥ 0.4 kg/h and ≤ 400 kg/h; the ability to generate a typical mean product particle size of ≤10 micrometers with existing fittings or by minimal modification of the spray-dryer with atomization nozzles enabling generation of the required particle size; and capable of being sterilized or disinfected in situ.
	Steam, gas or vapor sterilizable freeze drying equipment with a condenser capacity exceeding 10 kg of ice in 24 hours and less than 1000 kg of ice in 24 hours.
	Cross (tangential) flow filtration components (e.g. modules, elements, cassettes, cartridges, units or plates) with filtration area equal to or greater than 0.2 m2 for each component and designed for use in cross (tangential) flow filtration.
	Cross (tangential) flow filtration equipment capable of separation of pathogenic microorganisms, viruses, toxins or cell cultures without the propagation of aerosols, having all the following characteristics: a total filtration area equal to or greater than 1m2; andcapable of being sterilised or disinfected in-sito; or using disposable or single-use filtration components (excludes reverse osmosis and hemodialysis equipment, as specified by the manufacturer). ['sterilized' denotes the elimination of all viable microbes from the equipment through the use of either physical (eg steam) or chemical agents. 'Disinfected' denotes the destruction of potential microbial infectivity in the equipment through the use of chemical agents with a germicidal effect. 'Disinfection' and 'sterilization' are distinct from 'sanitization', the latter referring to cleaning procedures designed to lower the microbial content of equipment without necessarily achieving elimination of all microbial infectivity or viability.]
	Component: cultivation chambers designed to be sterilized or disinfected in situ
	Component: cultivation chamber holding devices
	Component: process control units capable of simultaneously monitoring and controlling two or more fermentation system parameters (e.g. temperature, pH, nutrients, agitation, dissolved oxygen, air flow, foam control).
	Centrifugal separators, capable of continous separation without the propagation of aerosols, having all the following characterisics: Flow rate exceeding 100 l/hr; components of polished stanless steel or titanium; one or more sealing joints within the steam containment area; and capable of in-situ steam sterilization in a closed state (includes decanters)

Picture copy from Council Regulation EC no 428/2009 on Dual use equipment and technology of concern

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Equipment used for testing vaccine efficacy in animal studies	
	Chambers designed for aerosol challenge testing with microorganisms, viruses or toxins and having a capacity of 1 m3 or greater.
	Nose-only aerosol exposure apparatus utilizing directed aerosol flow and having capacity for exposure of 12 or more rodents, or 2 or more animals other than rodents; and, closed animal restraint tubes designed for use with such apparatus.
PPE (sometimes used when handling large scale spills)	
	Protective full or half suits, or hoods dependent upon a the tethered external air supply and operating under positive pressure (not suits designed to be worn with self-contained breathing apparatus)
High containment units	
	Conventional or turbulent air-flow clean-air rooms and self-contained fan-HEPA filter units that may be used for P3 or P4 (BL3, BL4, L3, L4) containment facilities.
	Complete biological containment faciities at P3, P4 level
	Equipment: Breathing air suit decontamination showers
	Equipment: Mechanical-seal or inflatable-seal walkthrough doors
	Equipment: Double-door pass-through decontamination autoclaves
Isolators	
	Class III biosafety cabinets or isolators with similar performance standards (included flexible isolators, dry boxes, anaerobic chambers, glove boxes and laminar flow hoods (closed with vertical flow)
	Biocontainment chambers, isolators, or biological safety cabinets having all of the following characteristics, for normal operation: fully enclosed workspace where the operator is separated from the work by a physical barrier; able to operate at negative pressure; means to safely manipulate items in the workspace; iv.supply and exhaust air to and from the workspace is HEPA filtered. [Note 1 - this control includes class III biosafety cabinets, as described in the latest edition of the WHO Laboratory Biosafety Manual or constructed in accordance with national standards, regulations or guidance.] [Note 2 - this control does not include isolators specially designed for barrier nursing or transportation of infected patients]
“Catch-all” clause	
	Equipment and technology (not specified elsewhere in the control list of Dual-use Biological Equipment and Related Technology and Software) for the encapsulation of live pathogenic micro-organisms, viruses and toxins, with a typical mean product particle size of 10 μm or less.
Technology & knowledge	
	Transfer of 'technology' ('technical data') by any means, including electronic media, fax or telephone
	Transfer of 'technology' in the form of 'technical assistance'
Software	
	Controls on 'software' transfer only apply where specifically indicated in sections I and II above, and do not apply to 'software' which is either: Generally available to the public by being: Sold from stock at retail selling points without restriction, by means of: Over- the-counter transactions; Mail order transactions; Electronic transactions; or Telephone call transactions; and Designed for installation by the user without further substantial support by the supplier

Picture copy from Council Regulation EC no 428/2009 on Dual use equipment and technology of concern

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Key Messages

- Many types of vaccine production equipment are considered dual-use equipment.
- The only difference between a vaccine and a bioterror agent – is the final inactivation step
- Vaccine producers have a responsibility to control assets that might have interest for adversaries
- The Dual Use equipment should be handled in a way that proliferation does not occur.

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Conclusion

Vaccine producers already protect:

- ✓Information about their
  - ✓ *Bath sizes, yields*
  - ✓ *Number of lost batches/year*
  - ✓ *Batch documentation / production knowledge*
- ✓Final released product for sale
- ✓Seed lots / seed strains

It would only take a little extra effort to protect the access to intermediate non-inactivated products, production materials and equipment with dual use potential

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Action Plan

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KNOW		FEEL		BE ABLE TO DO	

Your learning doesn't stop with this lesson. Use this space to think about what else you need to do or learn to put the information from this lesson into practice.

What more do I need to know or do?	How will I acquire the knowledge or skills?	How will I know that I've succeeded?	How will I use this new learning in my job?

Thank You

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