

FEDERAL AND INTERNATIONAL PARTNERS IMPORT/EXPORT REGULATIONS WEBCAST



August 3 & 4, 2016



Centers for Disease Control and Prevention
Office of Public Health Preparedness and Response

WELCOME!

**FEDERAL and INTERNATIONAL
PARTNERS IMPORT/EXPORT
REGULATIONS WEBCAST**

August 3 & 4, 2016

12 PM – 4 PM EDT

Federal and International Partners

- Department of Agriculture, Animal and Plant Health Inspection Service (APHIS)
- Department of Commerce
- Department of Health and Human Services
 - Assistant Secretary for Preparedness and Response
 - Customs and Border Protection
 - Centers for Disease Control and Prevention
 - Division of Global Migration and Quarantine
 - Division of Select Agents and Toxins
 - Food and Drug Administration
- Department of the Interior, Fish and Wildlife Service
- Department of Transportation
- Public Health Agency of Canada

Agenda (August 4, 2016)

Time	Topic	Speaker
12:00-12:15	Greetings and Introductions	Lourdes Mueller
12:15-12:45	Canadian Import/Export Regulations	Cinthia LaBrie
12:45-1:15	Transporting Infectious Substances & Inspection Processes	Bill Stevens
1:15-1:45	Importing and Exporting CBER-Regulated Products	Kimberly Cressotti
1:45-2:15	The Zika Virus Response and Permitting Experience	Brent Davidson
2:15-2:30	Break	
2:30-3:15	Question/Answer Session	All
3:15-3:30	Closing Remarks	Mark Hemphill



Importing & Exporting Human pathogens and Toxins in Canada

Cinthia Labrie

Centre for Biosecurity, Public Health Agency of Canada

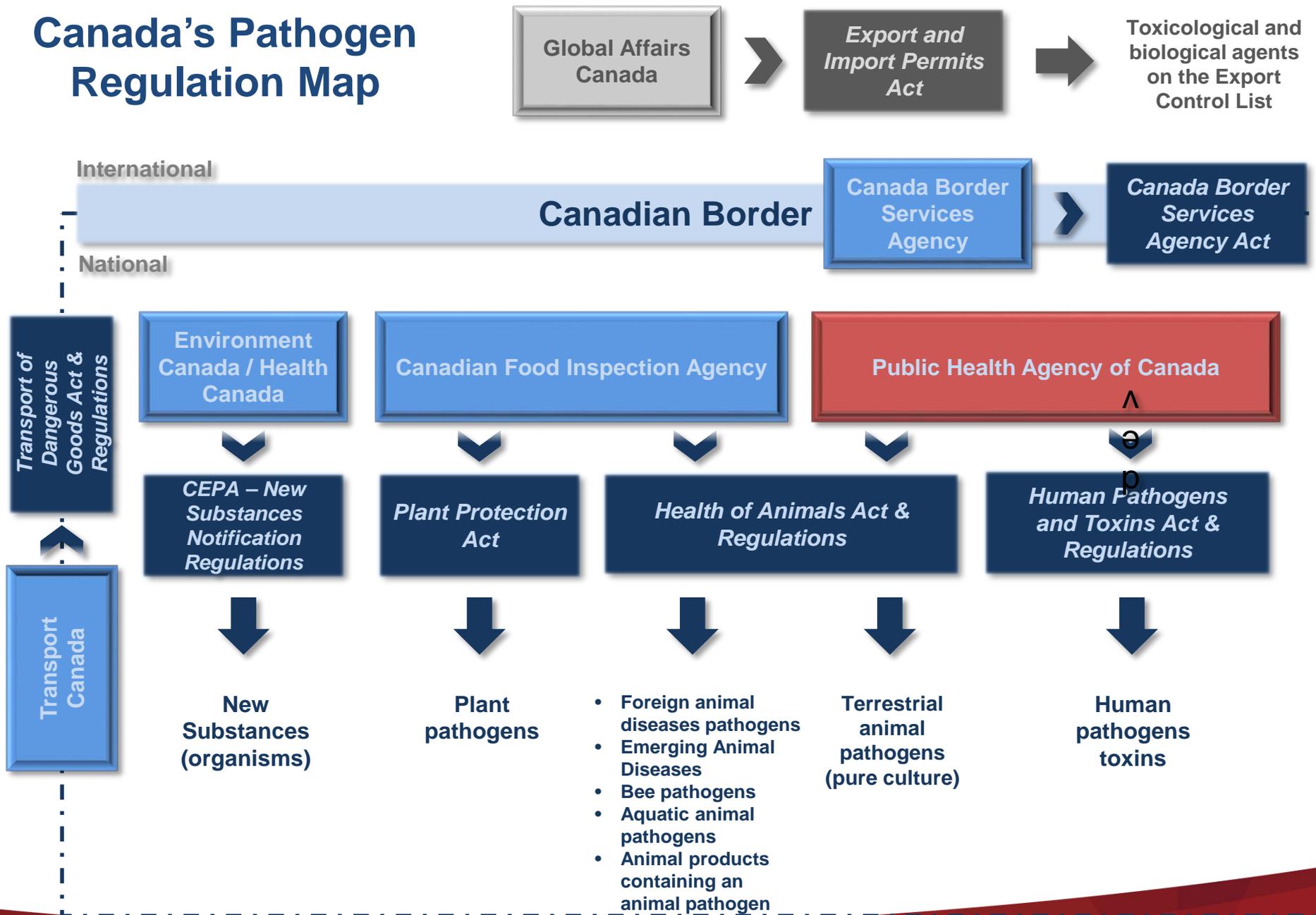
August 4th, 2016



Overview

- Overview of Pathogen Regulations in Canada
- Who We Are
- Acts & Regulations administered by our Centre
- Regulated Activities
- Exclusions and Exemptions
- Licensing Program
- Canadian Biosafety Standard
- Regulatory Documents
 - Importation permits
 - Letter to acknowledge receipt of an application
 - Pathogen & Toxin Licence

Canada's Pathogen Regulation Map



Who We Are



Centre for Biosecurity, Public Health Agency of Canada

Mandate

- To administer and enforce the *Human Pathogens and Toxins Act* (HPTA), the *Human Pathogens and Toxins Regulations* (HPTR) and the *Health of Animals Regulations* (HAR) to protect the health and safety of Canadians.

Our Acts & Regulations

- *Human Pathogens and Toxins Act*
 - Specific sections came into effect on June 23, 2009
 - Fully in force since December 1st, 2015
- *Human Pathogens and Toxins Regulations*
 - Came into effect on December 1st, 2015
- *Health of Animals Act and Regulations*
 - Select sections pertaining to importation and transfer of terrestrial animal pathogens indigenous to Canada

Overview of the HPTA

The *Human Pathogens and Toxins Act* (HPTA) provides new authorities to address risks posed by domestically acquired or produced human pathogens

Note: *Human Pathogens Importation Regulations* was repealed.

Key Features

- Common standards for all pathogen users
- Licenced activities
- Mandatory reporting of incidents
- Biological Safety Officer role
- Security clearances

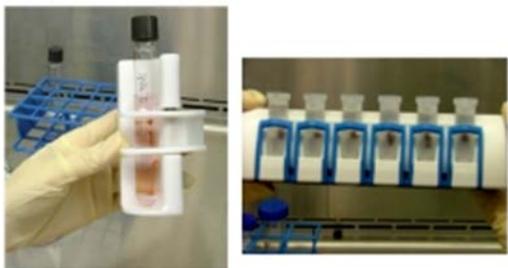
The HPTA does not apply to...

- Human pathogens and toxins that are in an environment in which they naturally occur, as long as they have not been cultivated or intentionally collected or extracted
- Risk Group 1 human pathogens
- Toxins not listed in Schedule 1

Activities that are covered under the HPTA

The HPTA **does apply** to :

- any **known** human pathogens or toxins that have been extracted, immunoprecipitated, concentrated, collected, amplified, cultivated, refined, cultured, and/or grown from such samples.



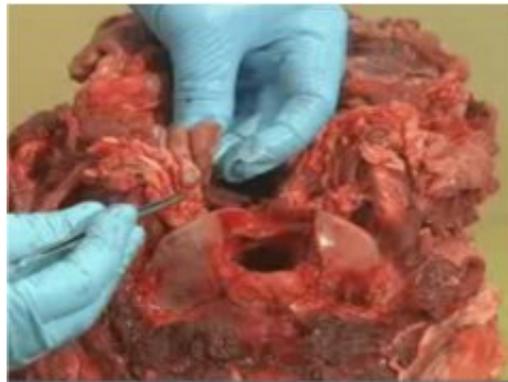
Immunomagnetic capture of organisms.



Exclusions from the Act – General Overview

The *Human Pathogens and Toxins Act* (Section 4) specifies that the Act does not apply to:

- » a human pathogen or toxin ***in an environment in which it naturally occurs if it has not been cultivated or intentionally collected or extracted.***
- » a drug in dosage form whose sale is permitted or otherwise authorized under the *Food and Drugs Act* or is in such a drug.



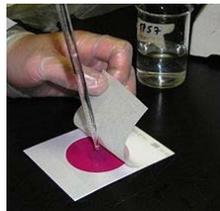
Exemptions

Under the *Human Pathogens and Toxins Regulations*, some controlled activities are exempt from the licensing scheme:

- laboratory analyses and/or diagnostic testing that are **not** producing a human pathogen
- laboratory analyses or diagnostic testing ***if production is done using a sealed container, and the container is decontaminated before disposal or reuse***



Parafilm



Petrifilm



- veterinarians conducting testing in a clinic

Note: Other sections of the *Human Pathogens and Toxins Act* still apply.

Commodity

Commodity	Regulated by PHAC	
	Yes	No
a) Pure culture – human pathogen	x	
b) Pure Culture – indigenous terrestrial animal pathogen	x	
c) Pure Culture – Exotic/Emerging animal pathogen *		x ⁽¹⁾
d) Pure Culture – Fish pathogen *		x ⁽¹⁾
e) Pure Culture – Plant pathogen *		x ⁽²⁾
f) Human sample or cell line (non infected)		x
g) Cell line containing a complete human pathogen	x	
h) Animal sample (healthy or infected)		x ⁽¹⁾
i) Monkey sample		x ⁽¹⁾⁽³⁾
j) Experimentally infected animal sample containing a human pathogen	x ⁽¹⁾⁽³⁾	

(1) May be regulated by Animal Health and/or Office of Biohazard Containment and Safety, Canadian Food Inspection Agency

(2) May be regulated by Plant Health, Canadian Food Inspection Agency

(3) May require a CITES permit

* If zoonotic, it will be regulated by PHAC as a human pathogen.

Licensing - PHAC Biosecurity Portal

The screenshot displays the PHAC Biosecurity Portal. At the top, there is a header with the Government of Canada logo and a search bar. Below the header is a navigation menu with categories: Jobs, Immigration, Travel, Business, Benefits, Health, Taxes, and More services. The main content area is titled "Biosecurity Portal" and includes a sidebar with a "Profile" link highlighted in a red box. The main content area features a "Biosecurity Portal" heading, a descriptive paragraph, and several "Topics" sections: "Licence applications", "Licences", "Reporting", "Biological agent search", and "Action items and notifications". The "Profile" link is also highlighted in a red box in the "Action items and notifications" section.

Government of Canada / **Gouvernement du Canada**

Search Canada.ca

Jobs ▾ Immigration ▾ Travel ▾ Business ▾ Benefits ▾ Health ▾ Taxes ▾ More services ▾

[Biosecurity Portal](#) → Biosecurity Portal

Biosecurity Portal

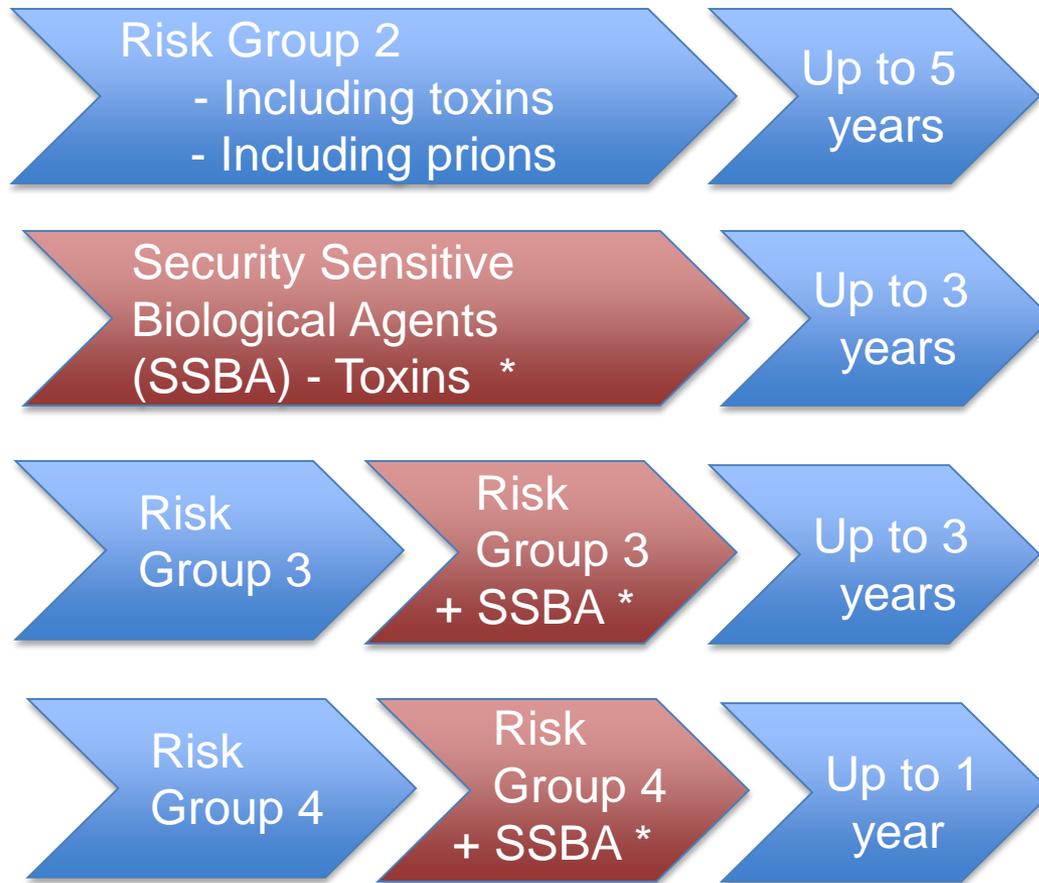
On this portal, you can apply for a licence under the *Human Pathogens and Toxins Act*, apply for an importation permit under the *Health of Animals Regulations* for terrestrial animal pathogens under the authority of the Public Health Agency of Canada; report an event; and, search for the risk group of a biological agent

Topics

- [Licence applications](#)
Apply for a new licence and access your submitted licence applications.
- [Licences](#)
Access, amend or re-apply for a licence.
- [Reporting](#)
Submit required reporting to the Public Health Agency of Canada.
- [Biological agent search](#)
Search our database to find the risk group of a biological agent.
- [Action items and notifications](#)
View a list of notifications and action items that require your action.

Profile
View and edit your profile, including the information you wish to receive from the Public Health Agency of Canada.

Risk-Based Approach for PHAC Pathogens and Toxins Licences



Any applicants conducting scientific research must submit a «Plan for the Administrative Oversight of Pathogens and Toxins in a Research Setting»

Known Risks:

- Inherent risks of a pathogen or toxin
- Increased risks linked to program intents
- Potential of certain organisms and toxins to pose a severe threat to public health
- Risks associated with scientific research and innovation
- Limited risk of work performed with quality control / testing panels
- Lowered risk of a pathogen or toxin that is in an environment in which it naturally occurs

**** Secret clearance required to access part(s) of the facility where SSBA are present (licence types identified in red)***

Licensing – General Overview

- An institutional licence will be required to conduct any controlled activities with human pathogens and toxins, unless they are specifically exempted.
- Licences have conditions, depending on the scope of an institution's controlled activities.
- Mandatory compliance with applicable requirements of the *Canadian Biosafety Standard*(CBS) is a common licence condition for all.
- Other conditions include:
 - not obstructing the Biological Safety Officer (BSO)
 - Requirements for importation, transfer and exportation
- Under the new licensing system, there will no longer be a requirement to apply for, and obtain, an importation permit.

PHAC Pathogen and Toxin Licence



Public Health
Agency of Canada

Agence de la santé
publique du Canada

No.
L-ST-43878-15-YS-00

Public Health Agency of Canada

Pathogen and Toxin Licence

Centre for Biosecurity / Centre de la biosûreté

(Name of Organization)

100 Colonnade Road, Ottawa, Ontario, K1A 0K9

(Address)

Security Sensitive Biological Agent Toxin Licence under section 18 of the *Human Pathogens and Toxins Act*

AND

Risk Group 2 Terrestrial Animal Pathogen Permit under section 160 of the *Health of Animals Regulations*

(Risk group covered by the Licence)

Subject to the conditions annexed hereto

Validity Period: 2015-12-01 to 2018-12-01, *unless otherwise suspended, varied, or revoked.*

Date Issued: 2015-11-25

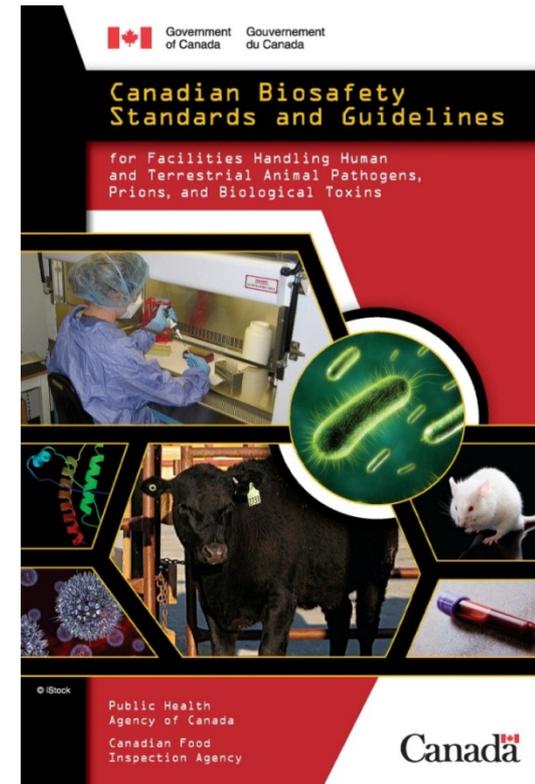
Issued to: Éleine Chatigny

Biological Safety Officer: Sandra Fry

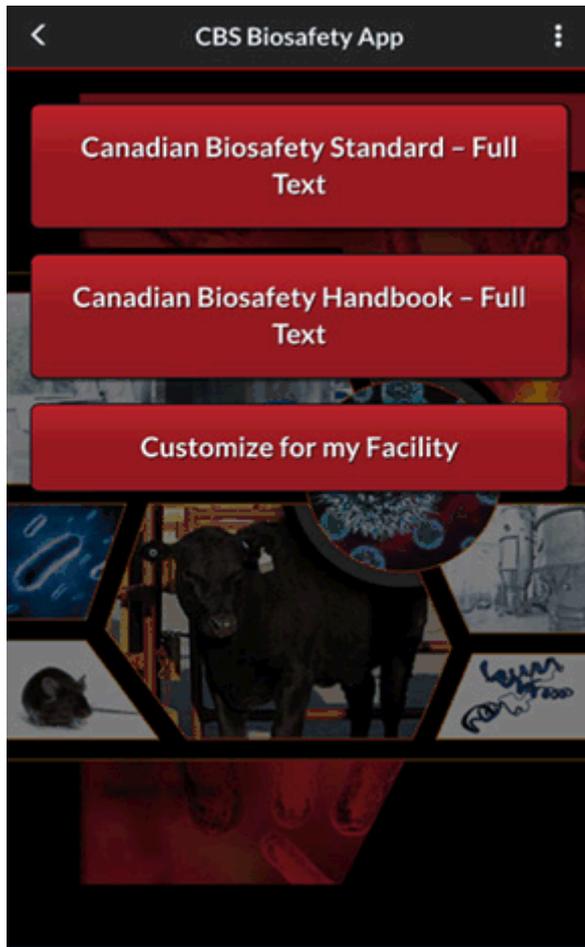
Canadian Biosafety Standard (CBS)

- The CBS is used by the Public Health Agency of Canada (PHAC) and the Canadian Food Inspection Agency (CFIA) to monitor and verify the ongoing compliance of regulated facilities with a licence for controlled activities with human pathogens and toxins or importing or transferring terrestrial animal pathogens.
- There is also a supporting guidance document
 - » *Canadian Biosafety Handbook (CBH)*
- New series of additional guidelines documents are being developed to further complement the CBS, CBH, and to further support the HPTA

canadianbiosafetystandards.collaboration.gc.ca
normescanadiennesbiosecurite.collaboration.gc.ca



CBS Biosafety App



Canada

3.1 Structure and Location

The site selection process for a **containment zone** generally includes an assessment of local programs and the local environment. Consideration of the **risks**, including the impact of possible **pathogen** or **toxin release**, is important at the beginning of the design phase and before construction work begins. In areas prone to natural disasters, buildings and support systems for containment zones may need to meet more stringent building codes.

3.1 Structure and Location		CL2	CL2-Ag	CL3	CL3-Ag
3.1.1	Containment zones to be separated from public and administrative areas by a door.	■	■	■	■
3.1.2	Dedicated paper/computer work stations within the containment zone to be segregated from laboratory work stations, animal rooms, animal cubicles	■	■	■	■

- Sort requirements based on Containment Level and work type
- Sort all biosecurity-related requirements
- Create checklists
- Save lists for different locations (e.g., laboratory, wing, or entire facility)
- Animated diagrams
- Android & Apple (available), web version coming soon

Regulatory Documents

- From December 2015 to December 2016, following the implementation of the new Act and Regulations, interested parties will see various documentation being presented for importation or exportation purposes.
 1. **Importation permit** delivered under the *Health of Animal Act and Regulations*
 2. **Letter to acknowledge the receipt of an application** (Licence Application #); provided to every organization who submitted an application through the portal between Dec1st, 2015 to February 29th, 2016 and confirmed existing activities could continue as is until reception of the actual Licence.
 3. **Pathogen and Toxin Licence**

1- Importation Permit format (until end of 2016)

 Public Health Agency of Canada		Agence de la santé publique du Canada		Permit no. / n° de permis P-15-XXXX
Permit to import human and/or terrestrial animal pathogen(s)		Permis d'importation d'agent(s) pathogène(s) humain(s) et/ou d'animaux terrestres		
Under the authority of the Human Pathogens Importation Regulations.		<input type="checkbox"/> Sous le régime du Règlement sur l'importation des agents anthropopathogènes.		
Under the authority of the Health of Animals Regulations		<input type="checkbox"/> Sous le régime du Règlement sur la santé des animaux.		
Importer-Name, address and postal code - Importateur-Nom, adresse et code postal		Facsimile-Télécopieur		Telephone no. - No. de téléphone
Attn:				
Supplier-Name and address - Fournisseur-Nom et adresse		Name(s) of Port(s) of Entry- To Clear Customs at Port(s) of entry Nom(s) du(des) point(s) d'entrée -Dédouanement au(x) point(s) d'entrée		
Description of Pathogen(s)-For the importation of-Description de l'(des) agent(s) pathogène(s)-Pour l'importation de				
Description of the pathogen				
On the following terms and conditions as marked- Selon les conditions indiquées:				
Conditions made under the authority of the Human Pathogens Importation Regulations and of the Health of Animals Regulations:		Conditions établies sous les régimes du Règlement sur l'importation des agents anthropopathogènes et du Règlement sur la santé des animaux:		
<ul style="list-style-type: none"> Work involving any of the imported material shall be limited to in vitro laboratory studies. All packaging materials, containers, equipment, animal pens, cages, bedding, waste and other articles under the importer's control, that come in direct or indirect contact with any of the imported material shall be decontaminated by a validated procedure. No work on the imported material shall be done, except work conducted or directed by the importer in the facilities described in the application for this permit. The imported material must be handled in accordance with the appropriate containment level requirements as described in the Canadian Biosafety Standards and Guidelines (1st Ed., 2013). On completion of the importer's work involving the imported material, all unused portions of the material and all its derivatives shall be destroyed by a 		<ul style="list-style-type: none"> Les travaux auxquels la matière importée est destinée doivent se limiter à des études de laboratoire in vitro. Le matériel d'emballage, les récipients, l'équipement, les enclos pour animaux, les cages, les litières, les déchets et tout autre article sous la responsabilité de l'importateur qui viennent en contact direct ou indirect avec la matière importée doivent être décontaminés en utilisant une méthode validée. La matière importée ne peut servir qu'aux travaux effectués ou dirigés par l'importateur dans les installations décrites dans la demande de permis. La matière importée doit être manipulée conformément aux exigences du niveau de confinement approprié décrites dans les Normes et lignes directrices canadiennes sur la biosécurité (1ère Ed., 2013). Au terme des travaux de l'importateur auxquels a servi le matériel importé, toute partie inutilisée du matériel et tous ses dérivés doivent être détruits en utilisant une méthode validée. 		

2- Acknowledgment letter

Attention | À l'attention de: Ms. Cinthia Labrie

Organization | Organisation: Centre for Biosecurity, 100 Colonnade Road, Ottawa, On K1A0Y9

Licence Application Number | Numéro de la demande de permis: **LA-15-0454461**

Activities | Activités: Prions, Risk group 2 pathogens and toxins, excluding Security Sensitive Biological Agent Toxins above trigger quantity | Prions, Agents pathogènes et toxines de groupe de risque 2, à l'exception des toxines d'agent biologique à cote de sécurité élevée en quantité supérieure à leur quantité seuil

Date Issued | Date de délivrance: 2015-12-31

Expiry Date | Date d'expiration: 2017-12-31, or until a licence is issued or denied | ou jusqu'à la délivrance d'un permis ou au refus de le délivrer

This correspondence serves to confirm that the Public Health Agency of Canada has received an application from the above-mentioned organization for a licence to conduct controlled activities under the Human Pathogens and Toxins Regulations (HPTR).

You are considered to be in compliance* with the HPTR and **may continue existing activities** with pathogens and toxins (**including import and transfer**) until a determination has been made about your application. The licence application number can be provided to the Canada Border Services Agency (CBSA) for the importation of human pathogens and toxins to facilitate the customs process. ...

3- Pathogen and Toxin Licence (1st page)



Public Health
Agency of Canada

Agence de la santé
publique du Canada

No.
L-ST-43878-15-YS-00

Public Health Agency of Canada

Pathogen and Toxin Licence

Centre for Biosecurity / Centre de la biosûreté
(Name of Organization)

100 Colonnade Road, Ottawa, Ontario, K1A 0K9
(Address)

Security Sensitive Biological Agent Toxin Licence under section 18 of the *Human Pathogens and Toxins Act*

AND

Risk Group 2 Terrestrial Animal Pathogen Permit under section 160 of the *Health of Animals Regulations*

(Risk group covered by the Licence)

Subject to the conditions annexed hereto

Validity Period: 2015-12-01 to 2018-12-01, *unless otherwise suspended, varied, or revoked.*

Date Issued: 2015-11-25

Issued to: Éleine Chatigny

Biological Safety Officer: Sandra Fry

3- Pathogen and Toxin Licence (2nd page)

No.
L-ST-43878-15-YS-00

ACTIVITIES HUMAN PATHOGENS AND TOXINS LICENCE

Subject to the conditions listed below, this licence authorizes the specified activities:

Activities	Biological Agents	Facility description	Type of Work Areas	Animal Species	Condition Names*
Disposing, Exporting, Handling, Importing, Permitting Access to, Possessing, Producing, Storing, Transferring, Using	Botulinum neurotoxin, Cholera Toxin, Staphylococcus enterotoxins, Types other than Type B	100 Colonnade, 100 Colonnade Road, Ottawa; 1120	Containment Level 2: Laboratory Work Area		Access to facilities, CBS CL2, In vitro, Prions prohibited, RG3/RG4 agent prohibited, Schedule 5
Disposing, Exporting, Handling, Importing, Permitting Access to, Possessing, Producing, Storing, Transferring, Using	Cholera Toxin	100 Colonnade, 100 Colonnade Road, Ottawa; 1124	Containment Level 2: Small Animal Zone	Camels (camelids), Skunks	Access to facilities, CBS CL2, In vitro/ Invivo, Prions prohibited, RG3/RG4 agent prohibited, Schedule 5

*See Conditions section at the end for full description details. You must also comply with the conditions stated under section 4 of the *Human Pathogens and Toxins Regulations*.

3- Pathogen and Toxin Licence (3rd page)

No.
L-ST-43878-15-YS-00

ACTIVITIES - TERRESTRIAL ANIMAL PATHOGEN PERMIT

Subject to the conditions listed below, this permit authorizes the specified activities:

Activities	Biological Agents	Facility description	Type of Work Areas	Animal Species	Condition Names*
Import, Move to another place	Toxins produced by animal pathogens	100 Colonnade, 100 Colonnade Road, Ottawa; 1120	Containment Level 2: Laboratory Work Area		Animal Introduction denied, CBS CL2, In vitro, Prions prohibited, Records, RG3/RG4 agent prohibited, Transfer under HAR

*See Conditions section at the end for full description details.

Contact Us

**CENTRE FOR BIOSECURITY
Public Health Agency of Canada
100 Colonnade Road AL: 6201D
Ottawa, Ontario
Canada
K1A 0K9
www.publichealth.gc.ca/pathogens**

Licences / permits

PHAC.permit-permis.ASPC@canada.ca

General Inquiries / HPTA related questions

PHAC.pathogens.pathogenes.ASPC@canada.ca



Transporting Infectious Substances Safely

CDC Webcast
August 3 & 4, 2016





Infectious Substances Guide





Objective

- Provide a general overview of the regulatory requirements for transporting Division 6.2 materials:
 - Package Selection
 - Marking and Labeling
 - Shipping Papers and Emergency Response Information
 - “Transportation” Security Plan and Training
- Inspection Process / Top Violations





Category A Infectious Substance

- UN2900, Infectious substances, affecting animals *only*, 6.2 (NO Tech name)
“or”
- UN2814 , Infectious substances, affecting humans, 6.2 (NO Tech name)

- **Category B Infectious Substance**
- UN3373, Biological substance, Category B, 6.2





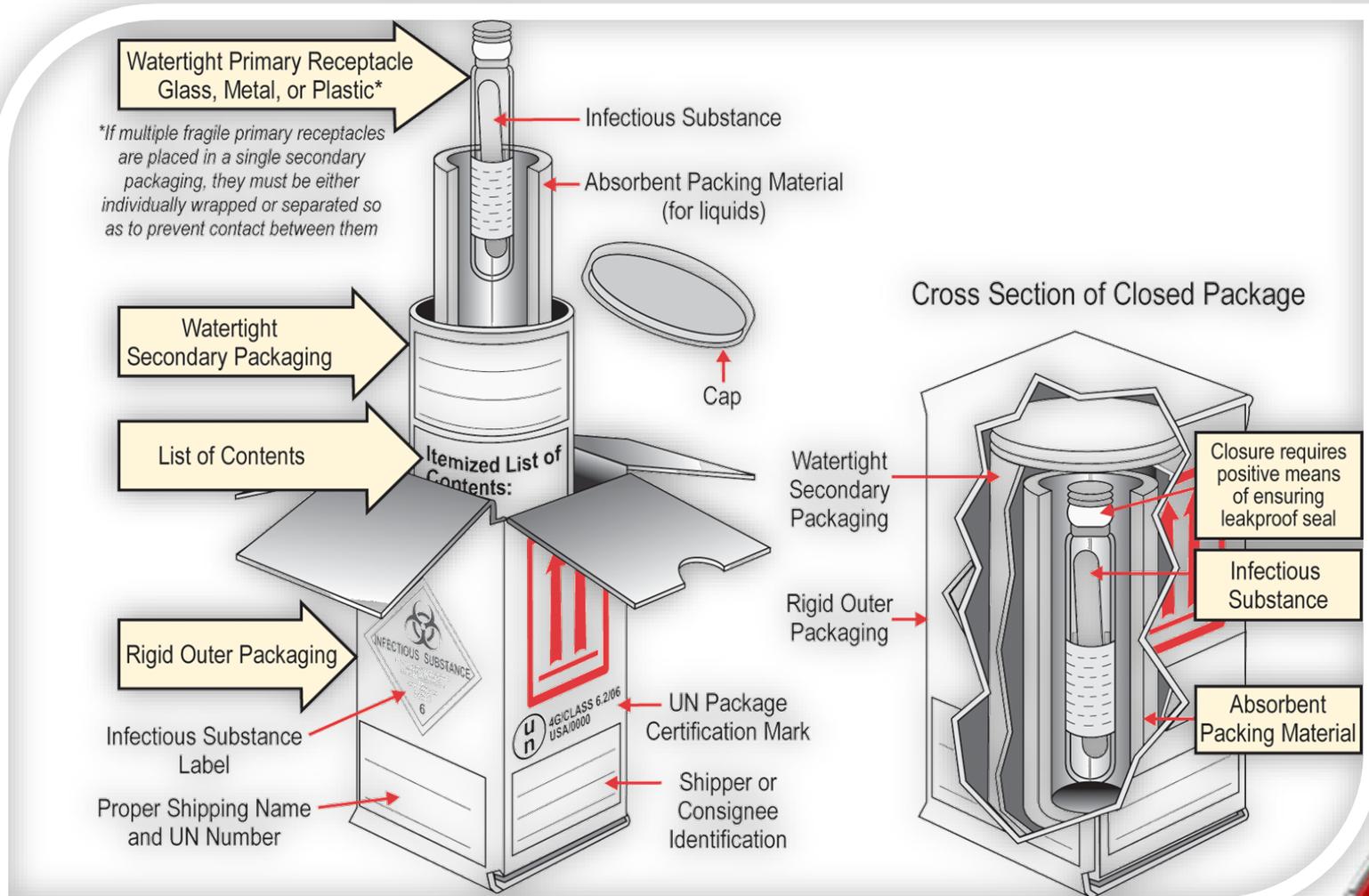
Packaging Requirements

Packaging Requirements	
173.24 173.24a 173.24a(c)	General Packaging Requirements for all HAZMAT Changes regarding Infectious Substances and mixed contents
173.134(b) 173.134(c)	Exceptions for: Division 6.2 Packaging Regulated Medical Waste
173.196	Category A Infectious Substance
173.197	Regulated Medical Waste
173.199	Category B Infectious Substance
178.609	6.2 Packaging Tests



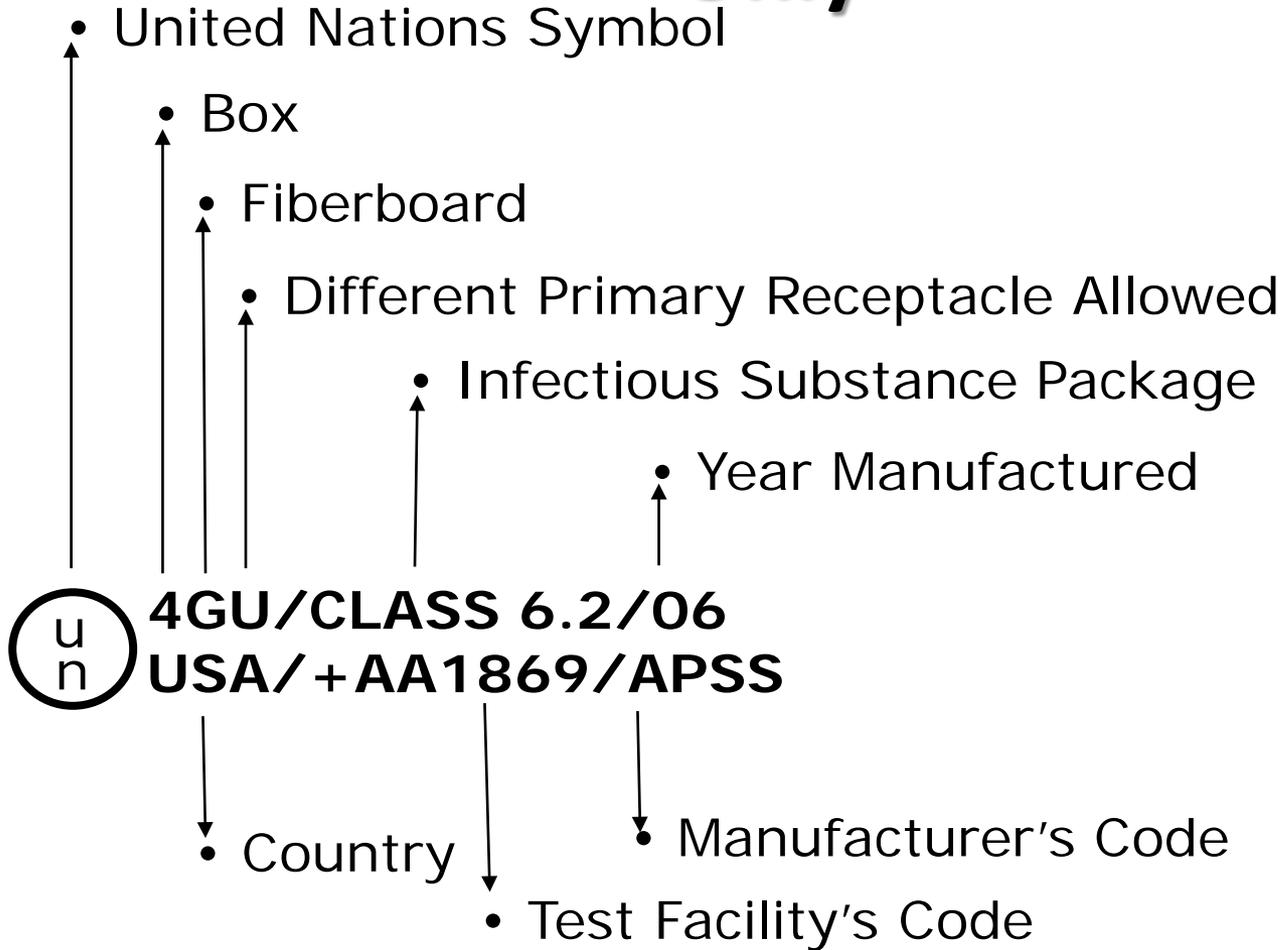


Category A Packaging





UN Packaging – Division 6.2 Category A Only





Testing of Packages

178.609

- Cat A Pkg: UN certified (4G or 4GU /Class 6.2)

Wet box for 1hr to represent 2" of rain per hr; then drop from 30 ft.

Freeze pkg 24 hr at 0 degrees then drop test.

Drop 1 ½" diameter, 15 lb steel rod, onto box or drop box onto steel rod.

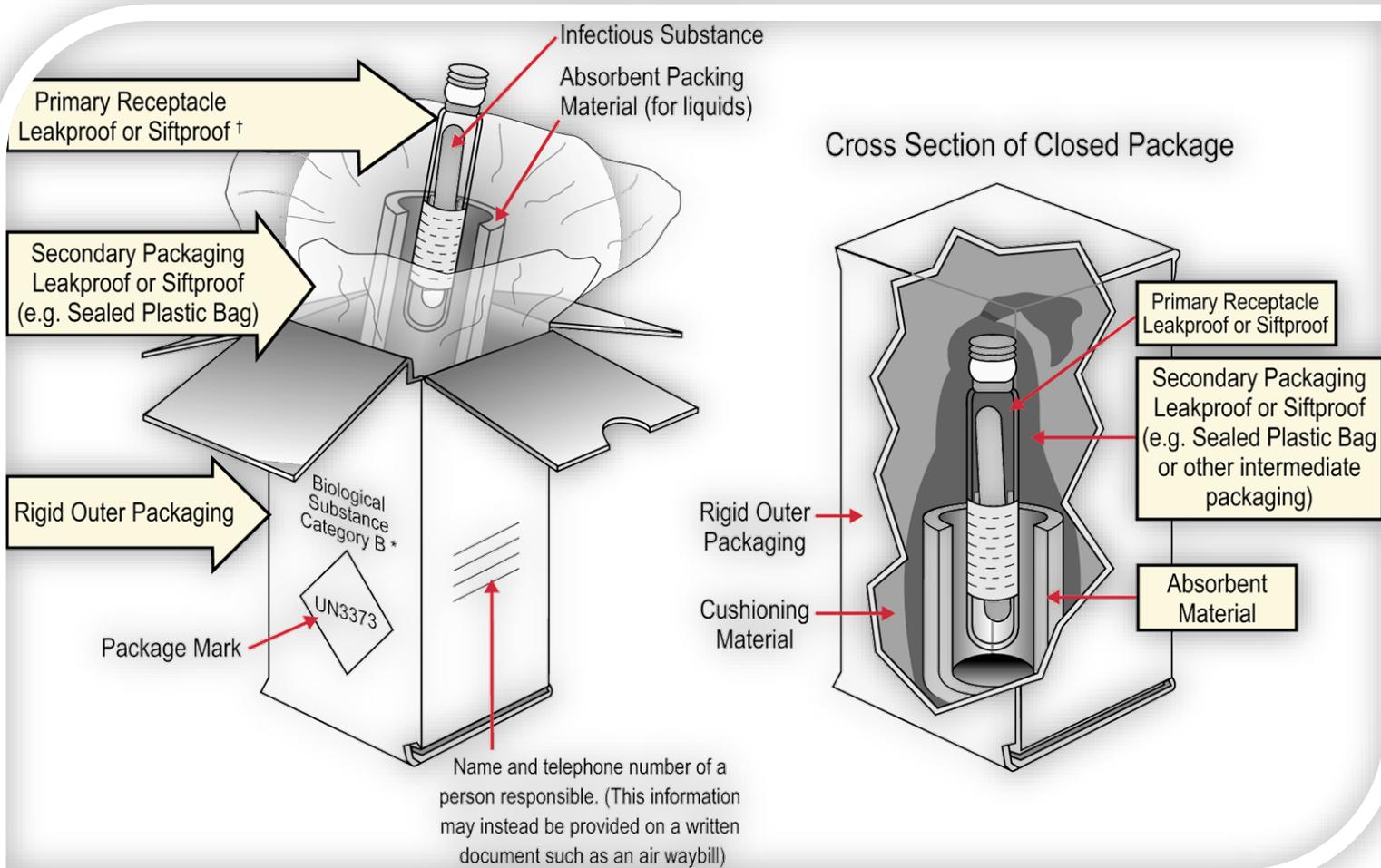
Dry Ice specific tests (if pkg intended to contain)

Variations "U": Smaller inner pkg; less number inner pkgs; fragile inner pkgs.





Category B Packaging





Cat “B” Non-Spec Package 173.199 Requirements Only

- Strong outer package
- Triple package – non tested.
- **Capable** of passing drop testing from 3.9 ft.
- Primary receptacles: Leakproof, will not break.
- Secondary receptacles: Secured within outer pkg
- Outer receptacles: Pkg prevents release of material
- Marking: **UN 3373**, Label “4 inch sides” (2” min)
- Name/address of person knowledgeable: Doc or pkg.
- Liquid Stabilizers: 1 oz/30 ml max.





Pkg Marking/Label Requirements

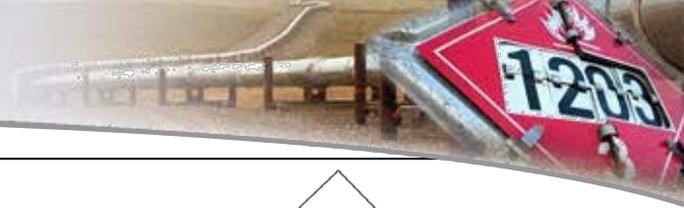
- **Category A**

- Proper shipping name & UN 2814 or UN 2900
(*No tech name on pkg per 172.301(b))
- Shipper or Consignee identification
- Infectious Substance Label 172.432 (Chgd 1 Oct 14)
- Orientation arrows (as applicable)

- **Category B**

- Proper shipping name and UN3373 Label
- Name and telephone number of responsible person
(may be placed on separate document such as air waybill)
- Orientation arrows (as applicable)





Labeling Requirements



& § 173.134(c)(d)



§ 172.432



§ 173.199(a)(4)
Category B infectious substance



§ 172.302
Bulk Marking (can also be on plain white placard)





Shipping Papers

- **Category A**
 - Identification Number
 - Proper Shipping Name / Tech Name
 - “Suspected Category A infectious substance” (Lost in the crowd concept)
 - Hazard Class/Division
 - NO Packing Group
 - Type Pkg/Unit of Measure (QTY)
 - Shipper’s Certification
 - Emergency Response Telephone Number
- **Category B (unless excepted)**
 - No shipping papers required





Emergency Response Information

- Requirements for providing and maintaining emergency response information identified in 172.602, Subpart G
- **On shipping paper - Stands out.**
- Exception: not required if a shipping paper is not required (Info: Shipper name/phone # on pkg or airway bill)



Photo: Lawrence Berkeley National Lab





Transportation Security Plan 172.802

- A “transportation” security plan is required:
 - Ship Select agents or toxins regulated by CDC or USDA (any amount)
- The plan must include:
 - Assessment of site/transportation security risks
 - Address personnel security, unauthorized access, and en-route security
 - Job titles, duties, training plan
 - Reviewed annually/revised as required





Other Training Requirements

- Federal hazmat transportation law 49 CFR, Part 172, Subpart H, requires training of *all* hazmat employees. Training must include:
 - General Awareness / Familiarization
 - Safety
 - Function Specific
 - Security Awareness
 - In-depth Security Tran Sec Plan (If Applicable)
- Anyone shipping infectious substances must have “knowledge and training”





Compliance Inspections

NO NOTICE!!!!!!

Introduction / Invite your representatives

Purpose / Tour facility: Inf Sub – Reg Med Waste – Chemical Waste

Packaging: Non-bulk, bulk, inner pkgng/liners,

Tested packages used (UN) (Pkgng is Our specialty)

Bills of Lading (Infectious Sub)

Training: Gen Aw/Function Spec/Sec Awareness/

Safety/Security plan (if required)

Security Plan (Select Agent Shippers only)

Exit Briefing: With or without violations noted.





Top Violations / Inspection Results

- Training
- Security Plan Requirements
- DOT/CDC Inspection Team – 300 + inspections since 2008
- Last 2 years been great. Minor violations.





Hazardous Material Info-Center

1-800-HMR-4922

(1-800-467-4922)

E-mail: infocntr@dot.gov

Hours of Operation: 9 am – 5 pm ET



- Obtain answers to HMR questions
- Request copies of Federal Register, special permits or training materials
- Report HMR violations
- Fax on Demand





Questions?

William Stevens **Investigator**

**Pipeline & Hazardous Materials Safety
Administration**

**Office of Hazardous Materials Safety
Field Operations - Southern Region**

**233 Peachtree Street, N.E. Suite 602
Atlanta, GA 30303**

**William.Stevens@dot.gov
(404) 832-1141**





Importing and Exporting CBER- Regulated Products

August 2016

Kimberly A. Cressotti
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality,
Division of Case Management
Biological Drug and Device Compliance Branch

Center for Biologics Evaluation and Research (CBER)

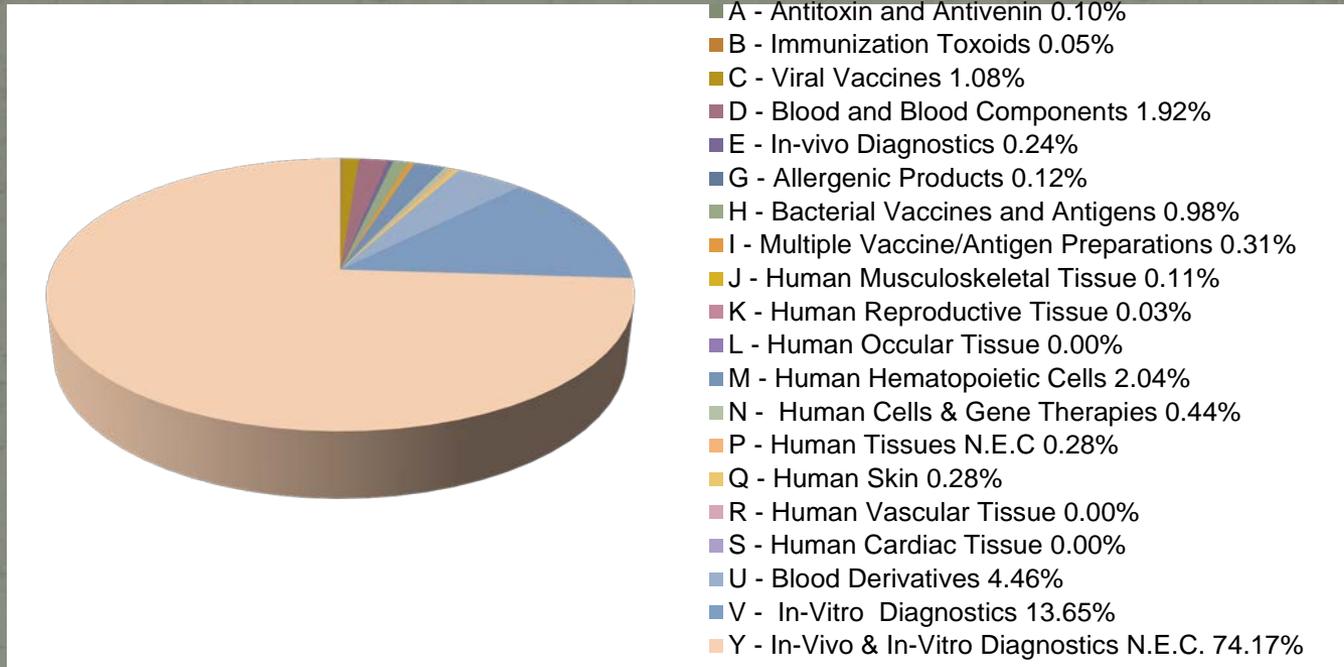
Regulates biological and related products, including blood and blood products, vaccines, allergenics, tissues, cellular and gene therapies, and some devices. For example:

- Antitoxins and Antivenins
- Vaccines
- Blood and Blood Components
- Blood-Derived Products
- Blood bags with anti-coagulant
- Certain devices involved in the collection, processing, testing, manufacture, and administration of licensed blood components, and cellular products, etc.
- All HIV test kits
- Allergenic Products
- Cellular products licensed under section 351 of the PHS Act
- Bone, ligaments, tendons,
- Eye/Ocular tissue
- Skin
- Arteries and veins
- Pericardium, heart valve allografts
- Reproductive tissue
- Hematopoietic stem cells from cord or peripheral blood

Imports – FD&C Act Section 801

Section 801 of the Federal Food, Drug, and Cosmetic Act (21 USC 381) sets out basic standards and procedures for FDA review of imports under its jurisdiction. Section 801(a) provides for examination of imports and also authorizes FDA to refuse admission of imports that appear, from examination or otherwise, to violate FDA requirements.

CBER-Regulated Imports



- CBER products constitute <1% of all FDA Imports
- FY2015: 150,674 CBER-regulated lines

CBER-Regulated Imports Cont.

- Compliance Program Guidance Manual 7342.007: Importation of biological products, drugs, and devices regulated under Section 351 of the PHS Act and/or FD&C Act
- 7342.007 Addendum: Importation of human cells, tissues, cellular, and tissue-based products (HCT/Ps) regulated under Section 361 of the PHS Act and 21 CFR Part 1271.

Importation: Special Circumstances

- Samples
- Biological specimens for research/testing
- Blood/blood components for autologous use
- Import-for-Export (IFE)

Samples

- Drugs (including biologics):
 - Intended solely for testing in vitro or laboratory research in animals if in compliance with 21 CFR 312.160
 - Blood grouping reagents, reagent red blood cells, and anti-human globulin for investigational in-vitro diagnostic use if in compliance with 21 CFR 312.160
- Devices (including biologics):
 - Intended for testing in vitro or in or on laboratory animals if in compliance with 21 CFR 812.5(c)
 - Shipments of IVDs for other research/testing purposes if in compliance with 21 CFR 809.10(c)(2)



Biological Specimens for Research/Testing

- Biological specimens NOT subject to FDA jurisdiction:
 - Used only for testing in a clinical laboratory or for basic scientific research
 - Not intended for the prevention, treatment, diagnosis, or cure of diseases, injuries, or conditions in humans, are not subject to FDA jurisdiction.
 - Three HTS Codes were recently updated to permit filers to disclaim entries of clinical specimens and reagents (3002905110, 3002100220, and 3002100290).



<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/BiologicsImportingExporting/ucm143371.htm>

Blood/Blood Components for Autologous Use

- Entries of unlicensed human blood or blood components for autologous use only may be imported if:
 - the manufacturer does not ship autologous blood products in interstate commerce on a routine or regular basis
 - the product(s) are for transfusion purposes only and have not been further processed or manipulated
 - the product(s) are properly labeled (see 606.121(i)(3),(4))

Import for Export

- Importation of certain articles that are unapproved or otherwise do not comply with the FD&C Act.
- The articles must be further processed or incorporated into products that will be exported from the United States by their initial owner or consignee
 - in accordance with section 801(e) or
 - section 802 of the Act or section 351(h) of the Public Health Service Act (PHSA).

Import for Export

- FDA must be provided certain information at the time of initial importation including:
 - A statement that confirms the intent to further process such article or incorporate such article into a product to be exported.
 - A statement that identifies entities in the chain of possession of the imported article.
- Types:
 - 801(d)(3): Drugs/Devices
 - 801(d)(4): Blood, Blood components, source plasma, source leukocytes

Admissibility Documentation that May be Requested

- Labeling for product
- Short supply agreement
- Import-for-Export Approval Letter under Section 801(d)(4) – where applicable
- Documents required by other agencies
- HCT/P accompanying records

Export

The imported product, which has been further manufactured, also must comply with applicable export requirements when the product is exported.

Export mechanisms:

- FD&C Act Section 801(e)
- FD&C Act Section 802
- 21 CFR 312.110
- PHS Act 351(h)

Export - FD&C Act Section 801(e)

801(e)(1):

Export of any food, drug, device, or cosmetic that is adulterated or misbranded under the FD&C Act unless it meets the specifications of the foreign purchaser, is not in conflict with the laws of the country to which it is intended for export, is labeled on the outside of the shipping package that it is intended for export, and not sold or offered for sale in the US.

801(e)(2):

Export of an unapproved device that doesn't comply with section 514 or 515 of the Act, is exempt from either such section under section 520(g) of the Act, or is a banned device under section 516 of the Act. FDA must determine that the device's exportation is not contrary to public health and safety, and has the approval of the country to which it is intended for export.

Export – FD&C Act Section 802

802(b)(1)(A):

Export of any drug, biological product, or device to any country if it complies with the laws of the importing country and has a valid marketing authorization in a “listed country.”

802(b)(2):

Export of unapproved/unlicensed drugs and biological products to an “unlisted country.” The product must comply with the laws of the foreign country and possess a valid marketing authorization by the responsible authority in that country. FDA must determine that the foreign entity has statutory or regulatory requirements pertaining to product safety and effectiveness, cGMPs, adverse event reporting, and labeling/promotion must be in accordance with the product’s approval.

Export – FD&C Act Section 802

802(b)(3):

Export of unapproved/unlicensed drugs and biological products to an “unlisted country” if the conditions for 802(b)(1)(A) and 802(b)(2) cannot be met. Scientific evidence must be submitted and reviewed by FDA and the foreign health authority to demonstrate that the products would be reasonably safe and effective. Exports via this mechanism are situation specific (i.e., they pertain to a specific drug intended for export to a specific country).

802(c):

Export of new drugs and biological products for investigational use in a “listed country.”

Export of Investigational Drugs and Biological Products - 21 CFR 312.110

- An IND is in effect, the product complies with the laws of the country to which it is being exported, and each person who receives the drug is an investigator of the IND; or
- FD&C Act Section 802(b)(1)(A) (see previous description); or
- FD&C Act Section 802(c) (see previous description); or
- The person exporting the product sends a written certification to the Office of International Programs which should affirm the items detailed in 21 CFR 312.110(b)(4); or
- A foreign national emergency necessitates exportation of the investigational product or the product is to be stockpiled in anticipation of a national emergency.

Export of Partially Processed Biological Products – PHS Act Section 351(h)

- Export of a biological product requiring purification, inactivation, fractionation, or significant chemical modification before being used in the formulation of a final product.
- The product must “not be in a form applicable to the prevention, treatment, or cure of diseases or injuries of man,” and not be intended for sale in the US.
- Intended for further manufacture into final dosage forms outside the US.

CBER Import/Export Team

For import compliance issues and information contact:

CBER/OCBQ: Division of Case Management:

- Robert Sausville, DCM Division Director
- Maria Anderson, MS, BDDCB Chief
- LCDR Shannon Aldrich, MPH
- Marc Alston, MS
- Lisa Andersen
- Kimberly Cressotti
- Jessica Dunn, PhD
- LCDR Monique Lester, MPH

CBERImportInquiry@hhs.fda.gov Phone # (240) 402-9155

CBER Import Website:

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/BiologicsImportingExporting/ucm143371.htm>

SHARING BIOLOGICAL MATERIAL DURING A PUBLIC HEALTH EMERGENCY AND THE PERMIT EXPERIENCE DURING THE ZIKA RESPONSE

Federal Partners Import/Export Regulations Webcast

August 4, 2016

Brent Davidson, JD
Branch Chief, International Assistance and Response Policy
Division of Internal Health Security
Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services

Outline

1. Introduction
2. Challenges to obtaining and sharing material related to pathogens causing a public health emergency
3. Experience of importing Zika-related samples during the response
4. Steps to address lessons observed



Responding to Infectious Disease Threats

- The Office of the Assistant Secretary for Preparedness and Response (ASPR) leads the nation in preventing, preparing for, and responding to the adverse health effects of public health emergencies and disasters
 - Global is the new local- threats abroad can be a threat to national and global health security
 - Most recent responses have been to novel and re-emerging infectious diseases with the potential to cause a **public health emergency of international concern**
- Rapid action is needed to **prevent and/or control** disease threats



Ebola
Zika virus
pH1N1
MERS-CoV

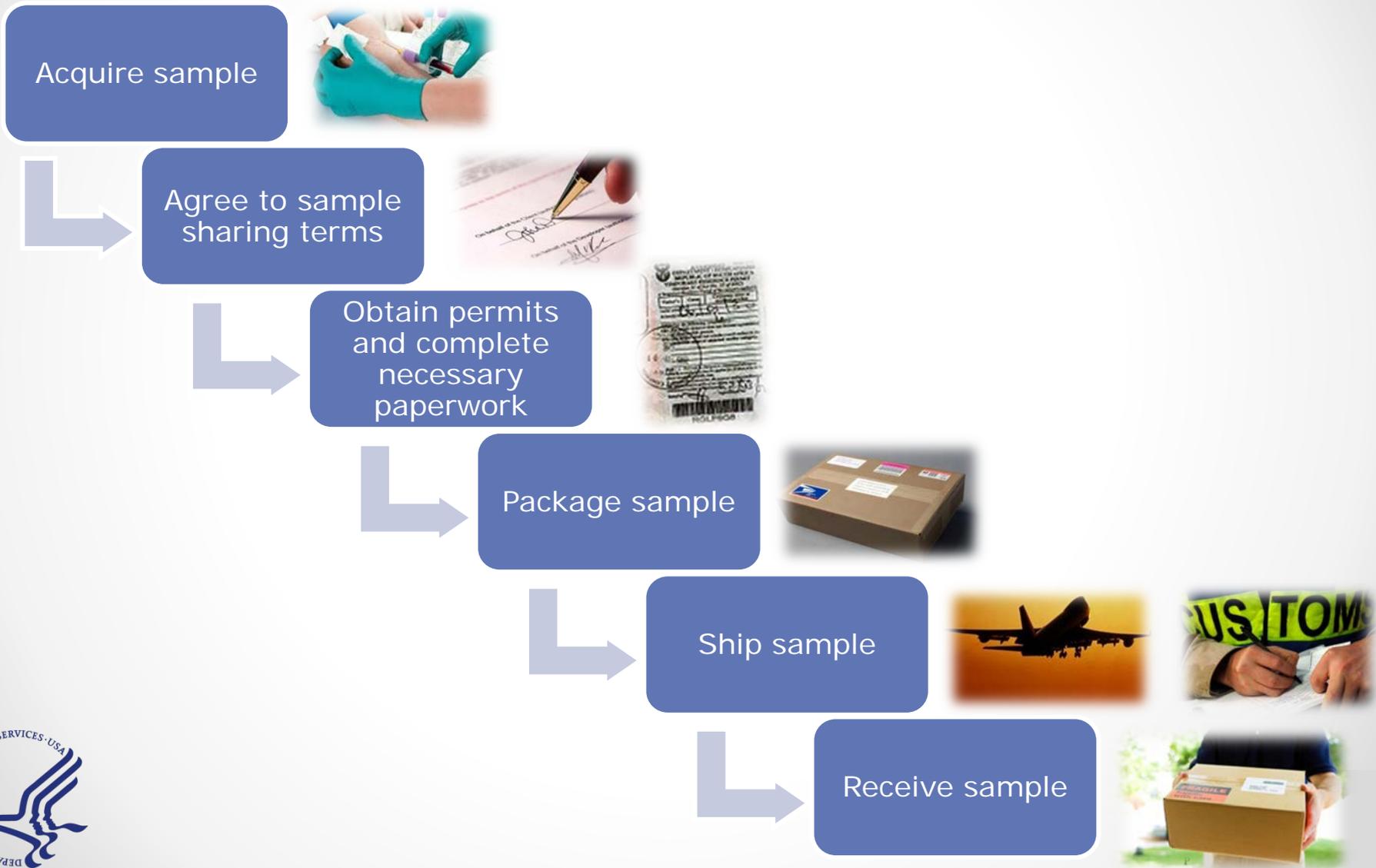


Rapid Sample Sharing During Public Health Emergencies

- Samples are critical for multiple types of research:
 - Basic research on pathogen/disease characteristics and epidemiology
 - Development of diagnostic assays, therapeutic drugs, and vaccines
- The research and public health response communities need **rapid access to samples** during a public health emergency
 - Without sharing material related to the emergency, scientists can't investigate how a new disease is spreading, or how it can be stopped.



Steps to Share Biological Material



Challenges to **Rapid** Sample Sharing During Emergencies

- Current policy and regulatory frameworks do not address the need to share samples rapidly, particularly for non-influenza related samples
- Routine processes generally not designed for emergency situations
 - No **flexibility** to adapt to an emergency situation (e.g. sample collection protocols for new pathogens in place, getting IRB approvals, etc.)
 - Not designed to work in the **timeframe** required during an emergency (e.g. negotiating material transfer agreements, obtaining import/export permits)
 - Delayed biosafety/biosecurity guidance to handle a novel or highly dangerous pathogen



Legal and Policy Challenges

- Patient privacy and consent
- Lack of an international agreement to share non-influenza samples
 - The **International Health Regulations** provide a legal framework for international cooperation which supports the sharing of biological material, **but** there are no existing international mechanisms to regulate and/or enforce the sharing of samples
 - **WHO Pandemic Influenza Preparedness Framework** only covers samples sharing during an influenza pandemic
 - Addresses benefit sharing (e.g. partnership contributions, SMTA)



Legal and Policy Challenges

- Access and benefit sharing concerns
 - Sovereignty of genetics resources
 - Intellectual property right concerns and commercial benefits derived from genetic resources
 - Nagoya Protocol
- Courier policy
 - Some international shipping companies will not transport infectious materials



Regulatory Challenges

- Import/export permits
 - Each country has different import and export regulations enforced (in many cases) by different authorities across government- identifying and obtaining permits can delay the import/export of samples
- Biosafety/Biosecurity concerns
 - Packaging samples in accordance with transport regulations- not all countries classify pathogens at the same threat level which can affect how a pathogen is packaged and shipped
 - Some pathogens must be studied in high-containment laboratory facilities- sample providers may need to confirm that the receiving laboratory is authorized to work with the samples



Logistical Challenges

- Transportation documentation
 - Shipping companies, international customs, and others may require specific documentation to accompany the shipment
- Pilot refusal
- Maintaining sample integrity
 - Cold chain



ASPR-led Collaborations to Address Sample Sharing Challenges

Domestic

- HHS Sample Sharing Working Group
 - Consulted on domestic and international policy and during potential or actual PHEICs
- Import/Export Tiger Team
 - Consulted on permit requirements

International

- Global Health Security Initiative (GHSI)
- North American Plan for Animal and Pandemic Influenza (NAPAPI)
- Beyond the Border Initiative (BTB)
- Global Health Security Agenda



Zika Experience: Background

In December 2015, what did we know?

- Suspected association between Zika virus and neurological defects such as microcephaly
- Virus spreading rapidly in the Americas
- Vector for Zika virus present in the United States
- Medical countermeasures:
 - **Diagnostics**- some available, but needed to be optimized for surveillance and clinical diagnostic purposes
 - **Vaccines**- none available
 - **Therapeutics**- none available



Zika Experience: Background

- ASPR convened a HHS Sample Sharing Working Group
- Priority sample needs:
 - 1: Obtain acute serum samples in order to **isolate Zika virus** for molecular diagnostic development and vaccine manufacturing purposes
 - 2: Obtain convalescent serum for **validation and verification of CDC serological assay** (IgM MAC-ELISA)
 - 3: Obtain convalescent serum for development of serology panels for use by commercial diagnostic manufacturers
 - 4: Obtain acute plasma for development of a NAAT for testing of the **blood supply**
 - 5: Additional research needs

We needed blood from individuals infected with Zika virus, at different stages of infection



Zika Experience: Background

- Sources of blood samples from Zika infected individuals and Zika virus isolates
 - **U.S. domestic travel-related cases:** Handful of travel related cases were identified, but contacting these individuals required intense coordination with state and local health departments
 - **U.S. territories:** Puerto Rico was experiencing local mosquito-borne transmission of Zika virus by December
 - **International:** Widespread local transmission of Zika in South and Central America (e.g., Brazil, Colombia, etc.,)
 - **Biorepositories** (for virus isolates): Isolates (particularly of older Zika virus strains) were being made available through several domestic and international repositories.



Importing Zika-Related Samples from International Partners

- Signed a Simple Letter Agreement (SLA), a type of Material Transfer Agreement, to obtain Zika virus isolates and serum specimens from individuals infected with Zika.
 - **Terms allowed use of the shared material for any legitimate public health purpose** (i.e. could use the sample for basic research, development of commercial diagnostics, etc.,)
 - **No restrictions on further distribution of the sample or its derivatives** (i.e. could distribute the material to whomever needed it)
 - Deposited clinical samples/virus at NIH-supported repositories and made the material accessible for both commercial and not-for-profit purposes



Importing Zika-Related Samples from International Partners

- Worked with USG Agencies (i.e. Tiger Team) to identify permit requirements
 - Permit from **U.S. Department of Agriculture (USDA)** required for the virus isolates due to use of fetal bovine serum (FBS)
 - A solution containing FBS was used to grow the virus isolates
 - Had to identify the source of the FBS to ensure the FBS was not sourced from a country with Bovine Spongiform Encephalopathy (BSE); if the FBS was sourced from a country that was not declared free of BSE, the sample would have had to go to USDA's Plum Island Animal Disease Center for additional testing.
 - Permit from **Centers for Disease Control and Prevention (CDC)** required for the human serum samples due to infectious nature of the sample



Importing Zika-Related Samples from International Partners



Importing Zika-Related Samples from International Partners

- Also needed a permit from the **U.S. Fish and Wildlife Service (FWS)** for the Zika virus isolates because the virus was grown in a VERO cell line
 - The VERO cell line is derived from the kidney of an African green monkey; it is one of the commonly used mammalian cell lines in microbiology
 - African green monkeys are protected by the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) against over-exploitation through international trade
 - In the United States, FWS carries out the provisions of CITES



Importing Zika-Related Samples from International Partners

- Bottom Line:
 - Successfully imported Zika samples, but **with delays**
 - Identifying permit requirements can be complicated
- What worked well:
 - Ongoing domestic and international efforts to identify “pain points” in the sample sharing process helped to identify the appropriate **points of contact** across the USG (i.e. Tiger Team) to identify import permit requirements, acquire permits and expedite sample import
 - These POCs helped to **expedite the process** of obtaining permits to import Zika-related samples



Lessons Learned to Avoid Delays in Obtaining Permits in an Emergency

- Obtain as much information about the sample that is being imported/exported
 - What are the **contents** of the sample (*e.g. does the sample contain a product from an endangered species*)?
 - What has the sample been **exposed** to (*e.g. was fetal bovine serum used, was the sample obtained from a region affected by foot and mouth disease, etc.,*)?
 - What will be sample be **used** for?
- Use this information to help identify U.S. permit requirements and work with the relevant offices to determine if a permit is required



Next Steps

- Continue to work domestically and internationally to develop mechanisms that facilitate sample sharing
 - Barriers to obtaining and sharing samples during a public health response are not limited to the delays in obtaining appropriate permits. Need to address:
 - Access and benefit sharing concerns
 - Delays caused by protracted negotiations of Material Transfer Agreements
- Domestically, ASPR is working with partners across the USG to develop a **USG Sample Sharing Framework**
 - Process for the USG to obtain and share samples for immediate public health priorities
 - Process for the USG to share samples with international partners



Closing Remarks

Mark Hemphill
Deputy Director,
CDC Division of Select Agents and
Toxins