IMPAACT 2013

PHARMACY CONSIDERATIONS

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Presentation Overview

- Study Activation Requirements
- Study products
- Packaging and Labeling
- Ordering and Shipment
- Storage
- Other required pharmacy supplies
- Aseptic preparation
- Chronology

- Diluent/ placebo preparation
- Vaccine preparation
- Dispensing/Transportation
- Accountability/CoC
- SNAP Freezing
- Destruction of syringes and needles
- Return of unused study product
Study Activation Requirement

- Site PoR must either have been certified for IATA shipment or have guaranteed access to non-study personnel to IATA qualified individuals
Study Product Sections

- Protocol: Study product section
- MOP: Study product section
- MOP Appendix VI- relevant forms
Study products/supplies from the CRPMC

- RSV vaccine (Live Recombinant Respiratory Syncytial Virus (RSV) D46/NS2/N/ΔM2-2-HindIII)
- Diluent/placebo (2X Leibovitz L-15 medium, 100ml bottle)
- Sterile oral 1ml syringes and caps
- Yellow overlays
Ordering Prerequisites

- Pharmacist have study specific training
- Site Protocol Registered
- Ordering instructions will be sent to the site pharmacist from the Clinical Research Products Management Center (CRPMC)
  - Drug Supply Statement
  - CRPMC Internet Ordering System (CIOS)
Shipping

- The vaccine and the 2X L-15 Leibovitz medium will be shipped in separate packaging, because they must be shipped at different temperatures.
Storage

RSV vaccine

- Transfer to freezer in order to maintain the specified storage temperature of \(-80 \pm 15^\circ C\).
  - Remove only when ready to prepare the dose after diluent preparation
  - Can not be refrozen or reused

Diluent

- Transfer to refrigerator temperature to maintain the specified storage temperature of \(2-8^\circ C\) \((36-46^\circ F)\). Do not freeze.
  - Open new container for each use

Any issues with the product must be immediately communicated with the CRPMC

SWFI

- Obtained by the site
- Must be cold when used
Prescription

- PID and SID number
- RSV vaccine or placebo
- Date and time the vaccine/placebo is to be administered
- Signature of an authorized prescriber
- The DAIDS PAB Pharmacy Guidelines for Clinical Trials Networks manual as well as all local regulations must still be followed for prescriptions
- Maintain blind
Supplies needed for vaccine/diluent/placebo preparation - sites to acquire

▶ See Appendix II in the MOP

<table>
<thead>
<tr>
<th>Supplies needed</th>
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<tbody>
<tr>
<td>Sterile Water for Injection, UPS, (SWFI)</td>
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<tr>
<td>Empty Sterile Vials 10 ml</td>
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<tr>
<td>Syringe Carrier Cases</td>
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<tr>
<td>Syringe bags Reclosable bag</td>
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<tr>
<td>Min-max thermometer</td>
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<tr>
<td>Water bath with a Thermometer</td>
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<tr>
<td>Empty Sterile Vials 30 ml</td>
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<tr>
<td>Sarstedt 2 ml Cryovials</td>
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<tr>
<td>Intranasal administration only label</td>
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<tr>
<td>Two-part label for oral syringes</td>
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<tr>
<td>Label for the syringe carrier bag</td>
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<tr>
<td>Cryovial labels – one type will be available from the CRPMC</td>
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<tr>
<td>Playmate Pal 7 qt. personal size cooler</td>
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<tr>
<td>Pelleted Dry Ice</td>
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<tr>
<td>Waterproof vial label</td>
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<tr>
<td>Beaker for wet ice</td>
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<tr>
<td>CoolBox 30 System</td>
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</table>
Consult with institutional infection control, hospital epidemiologist, or safety officer regarding appropriate aseptic preparation area to utilize

- Currently RSV products are classified as BSL2 agent
- Lab folks are working on getting RSV downgraded to BSL1.

Vaccine and placebo prep must be performed in a clean room, isolator or biosafety cabinet

DEPENDING ON YOUR ASEPTIC PREPARATION AREA SET UP THE APPROPRIATE CLEANING, SPRAYING AND WIPING IS TO FOLLOW USP 797 AND INSTITUTIONAL REQUIREMENTS

Depending on your set up, the wet ice maybe under the hood or on the bench. See protocol for preparing wet ice for use in the hood
Steps for study product preparation

Day Before Vaccine Preparation Make Sure:

Vials of SWFI in Refrigerator

Cool Rack in -20º Freezer
Steps for study product preparation

- Verify prescription for completeness
- Check randomization assignment
- Gather Ambient temperature supplies for vaccine/placebo preparation
  - Syringes-assorted sizes for 15 ml, 5 ml and 1 ml and small gauge needles
  - 2 Sterile oral syringes and caps and Yellow Overlays
  - Syringe cases, reclosable syringe carrier bags
  - Bags for ice
  - Sarstedt Cryovials
  - Sterile Empty vials 30 ml and 10 ml
  - Labels -2 part syringe label, waterproof vial labels, cryovial labels, bag label, and Intranasal Administration Only Label
  - Forms-Diluent, Placebo, Vaccine Prep; 2013 SPAR, vaccine aliquot
  - Cooler and Thermometers
PRACTICE VACCINE PREPARATION

- New pharmacist trainees must prepare a sample of the diluted and undiluted vaccine for QA/QC.

- After receipt of the DSS, ordering, and receiving study product pharmacy staff will conduct practice vaccine preparation and ship aliquots to Bhavin Thumar (bthumar@jhu.edu) according to protocol Section 5 and MOP Section 5.

- Ship aliquots on Monday, Tuesday or Wednesday.

- Notify Bhavin and cc: Kim Wanionek (kwanion1@jhu.edu) and Jen Oliva (joliva2@jhu.edu) that the aliquots are on the way so that the plates can be set up for replication.

- *Important note*: FedEx labels for shipping practice vaccine preparation aliquots will be provided to sites by the IMPAACT Operations Center. Sites must provide contact information (i.e., full name, shipping address, email address, phone number) for the person to whom shipping labels should be sent—please send this information to cperlowski@fhi360.org.

- A site will be activated to begin implementing study procedures only after the practice vaccine preparation has been deemed acceptable. It is hoped that any issues with the results can be resolved by phone.
<table>
<thead>
<tr>
<th>Activities for study product preparation day</th>
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<td>Place Cool Rack on dry Ice</td>
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<td>Prepare wet ice for use in BSC</td>
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<td>Prepare cooler with wet ice and thermometer for transport</td>
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<td>Prepare water bath</td>
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<tr>
<td>Prepare Diluent (and Placebo) before thawing vaccine</td>
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<tr>
<td>Thaw vaccine in water bath</td>
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<tr>
<td>Prepare vaccine</td>
</tr>
<tr>
<td>Transport vaccine to clinic in temperature monitored cooler</td>
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<tr>
<td>Prepare Aliquots</td>
</tr>
<tr>
<td>After all active vaccine preparation, aliquots must be shipped to JHU</td>
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</table>
First Prepare the diluent

- Remove 1 new unopened bottle of 2X L-15 from the refrigerator and note the time on the Diluent Preparation Form. Put on wet ice until ready to use.

- Put a 4-hour expiration time from the time the 2X L-15 was removed from the refrigerator on the 1X L-15 Label.

- Remove enough vials of sterile water for injection from the refrigerator to provide 15 mL.

- Verify that the products are not expired or opened and the solutions are clear.

- With a syringe, transfer 15 mL of 2X L-15 into the empty sterile vial.

- Add 15 mL of cold sterile water for injection to the vial to make 30 mL of 1X L-15 and mix well.

- Label this vial with the 1X L-15 label and place vial on wet ice.
DOCUMENT THE PREPARATION

- Document preparation on the Diluent Preparation Form.
- Remove the label from the 2XL-15 and place on the Diluent Preparation Form.
- Document the dispensing on the Study Product Accountability Record for 2XL-15.
PREPARE PLACEBO DOSE

IF THE DAY’S ADMINISTRATION(S) INVOLVE A PLACEBO, MAKE THE PLACEBO DOSE PRIOR TO MAKING ANY VACCINE DOSES

Prepare two 2-part syringe labels with the expiration time of 4 hours from when the 2X L-15 was removed from the refrigerator.

Label the plastic syringe bags with participant-specific labels and expiration time of 4 hours from when the 2X L-15 was removed from the refrigerator. Affix a “FOR INTRANASAL ADMINISTRATION ONLY” label to the bag.

Draw up excess of 0.5 mL of 1X L-15 from the vial labeled 1X L-15 Diluent into a 1 mL syringe.

Transfer 0.5 ml of the 1X L-15 into the sterile oral syringe

Cap the oral syringe and apply yellow overlay and place on wet ice
Syringe Case Considerations

- Order multiple syringe cases depending on how many participants will be inoculated on one day (2 per participant).
- Syringe cases can be reused but must be wiped down with alcohol between uses to avoid spread of RSV vaccine to placebo.
- Contrary to protocol and MOP, I think that the back-up dose should be placed in a syringe case, double bagged and labeled at the same time as primary dose to:
  - Avoid accidental discharge of dose.
  - Avoid accidental unblinding by not treating first and second dose exactly the same.
- (I didn’t change the MOP so that this is not “a must”.)
Vaccine preparation

- Withdraw 4.5 mL of 1X L-15 and inject into the empty 10 ml sterile vial
- Place both vials on the wet ice
- Remove 2 vaccine vials from the freezer. Verify vaccine name and lot number is correct and document removal time.
- Transport on dry ice if necessary.
- Rapidly, but carefully thaw vial in warm water bath (32°C) until a small ice pellet is left in vial.
- Uncap vials and combine the contents of one into the other vial.
- Recap and swirl to combine
- Withdraw 0.5 ml, recap vial and put back on ice, and add the 0.5 ml to the vial containing 4.5 ml of 1x L-15.
- Label $10^5$ PFU/0.5 ml and place on wet ice
PREPARE VACCINE DOSE

- Prepare two 2-part syringe labels with the expiration time of 4 hours from when the 2X L-15 was removed from the refrigerator.

- Label the plastic syringe bags with participant-specific labels and expiration time of 4 hours from when the 2X L-15 was removed from the refrigerator. Affix a “FOR INTRANASAL ADMINISTRATION ONLY” label to the bag.

- Draw up excess of 0.5 mL from the vial labeled diluted vaccine $10^5$ PFU/0.5 ml into a 1 mL syringe.

- Transfer 0.5 ml of the 1X L-15 into the sterile oral syringe.

- Cap the oral syringe and apply yellow overlay and place on wet ice.
Prepare Vaccine Dose

- Repeat to prepare the backup dose.
- Label each oral syringe with a two-part label.
- Place the oral dosing syringe in a syringe carrier case and put the syringe case in the labeled plastic syringe bag. Place the labeled zip lock bag containing the syringe in the syringe carrier in another re-sealable plastic bag and put the syringe bag into in a cooler on wet ice.
- Put the labeled backup dose in a case and double bag and keep it on wet ice or the refrigerator until it is determined that a replacement dose is not needed at the clinic.
- Document preparation on the Vaccine Preparation Form.
- **Transport study product** in a cooler maintained at 2°C - 8°C with min/max thermometer until administration to the participant.
Chain of Custody

For IMPAACT 2013 Chain of Custody is documented on the Study Product Administration Record

Document the temperature on the IMPAACT 2013 Study Product Administration Record (SPAR) when the cooler leaves the pharmacy and reset the min/max thermometer.

Note the expiration time along with the signatures of the pharmacy staff on the SPAR

The clinic staff must inspect the contents and sign the SPAR when the cooler is received at the clinic, along with the signature of the clinic staff receiving the cooler.

Clinic staff must document the current, minimum, and maximum temperatures on the SPAR when the vaccine dose is removed from the cooler for administration to the participant.

After the SPAR is returned to the pharmacy, PoR completes the bottom of the SPAR to document any returned syringes, photocopies for pharmacy records and returns original, completed form to the study coordinator for the study binder or ppt’s record.
SNAP Freezing

As soon as possible after the vaccine doses are dispensed, prepare aliquots of the remaining diluted and undiluted vaccine in Sarstedt 72.694.006 cryo vials.

All aliquots should be snap-frozen and stored at -80°C ± 15°C until shipped.

Snap freeze the Sarstedt vials using a CoolBox system (CoolBox with CoolRack, BioCision, Mill Valley, CA) and dry ice pellets.

Store the CoolRack in a -20°C freezer when not in use.
SNAP Freezing

Fill the CoolBox cavity with dry ice pellets up to the bottom of the finger grip recess.

Place the CoolRack directly onto the dry ice. This could be done before making vaccine as the CoolRack must be on dry ice for at least 20 minutes prior to preparing the Sarstedt cryovials.

Prepare 4 cryovial labels for the diluted vaccine with date and time aliquoted and frozen and site number.

Prepare 4 cryovial labels for the undiluted vaccine with date and time aliquoted and site number.

Prepare the labels clearly so that the vials do not have to be relabeled.
SNAP Freezing

Gather 6 Sarstedt vials, two 1 mL syringes, small gauge needles and labels and place in the BSC/isolator.

Withdraw from the $10^5$ PFU/0.5 mL diluted vaccine, 3 aliquots of 0.5 mL and put into 3 Sarstedt vials. Label with diluted vaccine cryovial label.

Withdraw all of the liquid from the $10^6$ PFU/mL undiluted vaccine, and divide it into 3 aliquots of at least 0.15 mL and put into 3 Sarstedt vials. Label with undiluted vaccine cryovial label.

If there is not enough vaccine for 3 aliquots of 0.15, then prepare 2 aliquots of 0.15 mL.

Ensure that the vials to be snap-frozen are tightly sealed. Care must be taken to tighten caps because CO2 from dry ice will affect pH of vial content and inactivate virus.
SNAP Freezing

Transfer the Sarstedt cryovials to the CoolRack in the BioCision CoolBox.

Leave the vials in the CoolBox for at least 15 minutes.

After the vials are frozen, take them out of the CoolBox and store the frozen vials at -80°C±15°C, separate from the study vaccine product in the Investigational Pharmacy freezer.

One aliquot of diluted and undiluted vaccine should be shipped to JHU the next available shipping day (Monday, Tuesday or Wednesday).

Allow dry ice to dissipate in the CoolBox. Do not throw dry ice in the sink. Extreme cold (dry ice) will crack the drainage pipe.

Place the extra aliquot labels on the Vaccine Aliquot Log. Enter stock vial numbers of the vaccine used, SID number(s) of participant(s) receiving the vaccine, and your initials.

Remove the labels from the original undiluted vaccine vials and place on the Vaccine Preparation Form.
Aliquot Shipping

For each participant receiving active vaccine, the pharmacy must batch ship 1 aliquot of diluted frozen vaccine and 1 aliquot of undiluted frozen vaccine on dry ice.

Ship all vaccine aliquots on the earliest available shipping day (Monday, Tuesday or Wednesday) after preparation. Care should be taken not to unblind the study staff when shipping vaccine aliquots.

Log out the aliquots to be sent from the Vaccine Aliquot Log by locating the correct aliquot label on the form and writing the date the sample is sent and your initials. Copy that page of the Vaccine Aliquot Log and include in the shipment.

Pack in a cooler with dry ice.

Fill out and include in the shipment the Investigational Drug Packing Slip – Vaccine Aliquots
Complete the FedEx Airbill - must fill out section 6, check Yes, Shipper’s Declaration NOT required.

Check ✓ Dry Ice and indicate quantity of dry ice in Kg.

The following labels must be attached to the shipping box:
- UN3373, Biological Substance, Category B
- UN1845: Fill in the amount of Dry Ice in Kg

Because only the active vaccine is snap-frozen, it is important that other study staff not be involved in the snap freezing and shipment from the pharmacy.

If the pharmacy gets the dry ice from the lab or the CoolBox from the clinic, in order to maintain the blind, the pharmacy should receive these supplies each day that doses are prepared. The dry ice can be discarded in the pharmacy if not needed.

Because it will take longer to prepare the vaccine dose than the placebo dose, the pharmacy should hold the placebo dose in the pharmacy longer to match the time it would take to prepare an active vaccine dose.
Study Products: Management

- Any remaining, unused vaccine/placebo syringes should be disposed of by incineration or placing in a solution of 1 part bleach to 9 parts water for 30 minutes and then disposed of as medical waste in accordance with site/institutional/local guidelines.

- Disposal of and/or destruction of USED AND UNUSED vaccine/placebo vials, needles, and syringes used in preparation must be in accordance with site/institutional/local guidelines for disposal of Biosafety Level 2 materials.

- Expired study product or product remaining at the end of the study should be retained at the site pharmacy until instructions are received from study sponsor, CRPMC, or Pharmaceutical Affairs Branch (PAB) to be returned to the CRPMC.