PHARMACY MANUAL

PEMBROLIZUMAB (MK-3475)

KEYNOTE 0XX

Add appropriate protocol number

Merck Sharp & Dohme Corp., NJ, USA
# SUMMARY OF REVISIONS

The following are a list of revisions to the Pharmacy Manual for pembrolizumab (MK-3475):

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revisions to Document</th>
<th>New Version #</th>
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<tbody>
<tr>
<td>10-Dec-14</td>
<td>Global change: updated MK-3475 to pembrolizumab</td>
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<tr>
<td>10-Dec-14</td>
<td>Global change: Inserted header Pembrolizumab (MK-3475) Pharmacy Manual for Investigational Studies</td>
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<tr>
<td>10-Dec-14</td>
<td>Expanded table of contents</td>
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<tr>
<td>10-Dec-14</td>
<td>Removed trailing zeros after decimal points</td>
<td>2.0</td>
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<tr>
<td>10-Dec-14</td>
<td>Section 2: Revisited footnote 1 in trial treatment table</td>
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<tr>
<td>10-Dec-14</td>
<td>Section 3.1: Removed text, “The pH is maintained using a 10 mM histidine buffer”</td>
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<tr>
<td>10-Dec-14</td>
<td>Section 3.2: Added text to emphasize normal saline as preferred diluent</td>
<td>2.0</td>
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<tr>
<td></td>
<td>Insert cautionary statement regarding drug transport and delivery</td>
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<tr>
<td>10-Dec-14</td>
<td>Section 3.3: Clarified weight based dosing calculation for changes in weight (10% rule)</td>
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<td></td>
<td>Removed calculation for 200 mg fixed dosing</td>
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<tr>
<td>10-Dec-14</td>
<td>Section 3.4: Clarified preferred method of dose preparation as volumetric reconstitution</td>
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<td>Clarified reconstitution technique.</td>
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<td>Section 3.6: Inserted text stating infusion rates may differ for</td>
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<td>Section 4.5:</td>
<td>Inserted text stating infusion rates may differ for infusion reactions</td>
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<td></td>
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<td>Inserted text that entire bag needs to be dosed during infusion</td>
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<td>Removed text regarding excess volume preparation</td>
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<tr>
<td></td>
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<td>Added text to document volume administered per DEG instructions</td>
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<tr>
<td>21-Oct-15</td>
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Template Version 5.0
21-Mar-2018
Study Version X.X
DD-MM-2018
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<td>21-Oct-15</td>
<td>3.2</td>
<td>Text added to footnote 2 for sourcing and recording of lot number, manufacturer, and expiry date.</td>
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<td>Added guidance for collection of the following diluent information (manufacturer, lot, and expiry).</td>
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<td>Removed the following text, “ unless instructed by the sponsor in writing” in the following sentence:</td>
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<td>Pembrolizumab (MK-3475) SHOULD NOT BE MIXED WITH OTHER DILUENTS unless instructed by the SPONSOR in writing.</td>
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<td></td>
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<td>Added diluted drug product in the following sentence:</td>
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<td>21-Oct-15</td>
<td>3.3</td>
<td>Section 3.3:</td>
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<td>Clarified re-calculation of weight based dosing guidance.</td>
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<td>Additional text added for concentration range requirements.</td>
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<td>21-Oct-15</td>
<td>3.7</td>
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<td></td>
<td></td>
<td>Removed chemotherapeutic waste designation for solution remaining in vials that must be discarded.</td>
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<td>Section 4.5: Added the following text regarding infusion set materials:</td>
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<td></td>
<td>*Contact Sponsor for materials not listed above</td>
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<td>21-Oct-15</td>
<td>Section 4.6: Added text for discarding used vials.</td>
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<td>28-Feb-17</td>
<td>Section 2.0: Updated footnote in trial treatment table to include SmPC and guidance regarding locally sourced drug.</td>
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<td>28-Feb-17</td>
<td>Section 3.1</td>
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<tr>
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<td>Section 3.2</td>
<td>Added text stating formulation is latex free</td>
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<td></td>
<td></td>
<td>Added rounding guidance.</td>
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<td></td>
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<td>Added guidance on temperature excursions.</td>
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<td>Clarified 4 hour room temperature time limitation.</td>
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<td>Updated language around particulates.</td>
<td></td>
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<tr>
<td>28-Feb-17</td>
<td>Section 3.3</td>
<td>Updated units from lb to kg to align with weight based dosing examples.</td>
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<tr>
<td>28-Feb-17</td>
<td>Section 3.4</td>
<td>Clarified use of biosafety cabinets.</td>
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<td>Updated gravimetric dosing guidance.</td>
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<td></td>
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<td>Added statement for use of spikes.</td>
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<td>Updated text for potential for foaming.</td>
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<tr>
<td>28-Feb-17</td>
<td>Section 3.5</td>
<td>Deleted duplicate text regarding use of biosafety cabinets.</td>
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<td>Updated text regarding formation of particulates.</td>
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<td>28-Feb-17</td>
<td>Section 3.6</td>
<td>Added guidance for preparation of placebo.</td>
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<tr>
<td>28-Feb-17</td>
<td>Section 3.7</td>
<td>Added instructional text that states 250mL volume is only applicable to weight based studies.</td>
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<tr>
<td>28-Feb-17</td>
<td>Section 3.8</td>
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<tr>
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<td>4.1</td>
<td>Clarified instructions for return of un-used vials. Added text stating formulation is latex free. Updated cap color for liquid formulation.</td>
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<td>28-Feb-17</td>
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<td>Added rounding guidance. Added guidance on temperature excursions. Clarified 4 hour room temperature time limitation. Updated language around particulates.</td>
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<td>Date</td>
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| 28-Feb-17  | Section 4.7  
Clarified instructions for return of un-used vials.                                                                                                                                                        |
| 21-Mar-2018| Section 1.0:  
Added unblinded clinical scientist to contact list  
Updated CDS title to CS  
Updated IVRS to IRT throughout document                                                                                                           |
| 21-Mar-2018| Section 3.2  
Added text for temperature excursions that temperature data needs to be included in clinical complaint.  
Clarified for blinded studies that uCRA should be contacted for temperature excursions.  
Updated the room temperature allowance from 4 hours to 6 hours and clarified fridge time allowance.  
Clarified the start of room temperature time.                                                                                                    |
| 21-Mar-2018| Section 3.6  
Revised flushing statement.  
Section 3.7  
Updated drug destruction instructions.                                                                                                              |
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<tr>
<td>21-Mar-2018</td>
<td>4.4</td>
<td>Updated room temperature time allowance to 6 hours and clarified cumulative storage time.</td>
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<tr>
<td>21-Mar 2018</td>
<td>4.5</td>
<td>Revised flushing statement.</td>
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<tr>
<td></td>
<td>4.6</td>
<td>Updated drug destruction instructions.</td>
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</table>

For the summary of changes/table of contents, teams should only use the content specific for their study, delete irrelevant sections.

**RED TEXT: Instructional/guidance text. Please delete before finalization and remove the “DRAFT” watermark.**
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*TEMPLATE DOES NOT ADJUST PAGE NUMBERS; PLEASE MANUALLY FINALIZE PAGE NUMBERS BEFORE FINALIZATION*
1. Contact List

Merck Sharp & Dohme Corp., NJ, USA (Pharmacy Manual questions only)

For questions regarding the details outlined within this Pharmacy Manual, please contact your clinical scientist (CS)

CS name, [Title]
Phone: [Phone #]
Fax: [Fax #]
E-mail: [E-mail]

For questions regarding the unblinded component of the study, please contact your Unblinded Clinical Research Associate (uCRA) and include the Unblinded Clinical Scientist (uCS) for emergent issues:

uCRA name, [Title]
Phone: [Phone #]
Fax: [Fax #]
E-mail: [E-mail]

IRT delete if not applicable

[Contact Name], [Title]
Phone: [Phone #]
Fax: [Fax #]
E-mail: [E-mail]
2. Trial Treatment

*Inserted per protocol by Protocol CS – refer to the trial treatment section in the protocol core; include all medications in the protocol (Example below):*

Trial Treatment Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Potency</th>
<th>Dose Frequency</th>
<th>Route of Administration</th>
<th>Regimen/ Treatment Period</th>
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<tr>
<td>pembrolizumab (MK-3475) 1</td>
<td>2 or 10 mg/kg</td>
<td>Q3W</td>
<td>IV infusion</td>
<td>Day 1 of each cycle 1</td>
<td>Experimental</td>
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<td>Paclitaxel 2</td>
<td>200 mg/m²</td>
<td>Q3W</td>
<td>IV infusion</td>
<td>Day 1 of each cycle</td>
<td>Treatment of cancer</td>
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<td>Bevacizumab 2</td>
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<td>Treatment of cancer</td>
</tr>
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<td>Ipilimumab 2</td>
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<td>Q3W</td>
<td>IV infusion</td>
<td>Day 1 of each cycle</td>
<td>Treatment of cancer</td>
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<td>Gefitinib 2</td>
<td>250 mg</td>
<td>Daily</td>
<td>PO</td>
<td>Daily</td>
<td>Treatment of cancer</td>
</tr>
</tbody>
</table>

1 Refer to protocol for specific study drug administration sequence for combination studies of pembrolizumab (MK-3475) and chemo/immunotherapy

2 Refer to local product label/SmPC for drug preparation and administration instructions; For any commercially available product that is provided by the trial site, subsidiary or designee, every attempt will be made to source these supplies from a single lot/batch number. Local guidelines should be followed for collection of locally sourced product information such as manufacturer, lot and expiry, unless otherwise instructed by sponsor. When the product is provided by Merck, the drug accountability log should be used for collection of this information
Retain Section 3 if study is utilizing pembrolizumab (MK-3475) powder formulation for infusion (e.g., Materials A, B or B'), otherwise delete all of Section 3

3. Drug Preparation – Pembrolizumab (MK-3475) Powder for Solution for Infusion, 50 mg/vial

3.1 DRUG PRODUCT

- Pembrolizumab (MK-3475) Powder for Solution for Infusion, 50 mg/vial

- Pembrolizumab (MK-3475) Powder for Solution for Infusion is a sterile, non-pyrogenic lyophilized powder for intravenous infusion supplied in single-use Type I glass vial containing 50 mg of pembrolizumab (MK-3475). The product is preservative-free, latex free, white to off-white powder and free from visible foreign matter.

- Pembrolizumab (MK-3475) Powder for Solution for Infusion is reconstituted with 2.3 mL sterile water for injection (WFI) to yield a 2.4 mL solution containing 25 mg/mL of pembrolizumab (MK-3475) at pH 5.2 – 5.8.

- Pembrolizumab (MK-3475) Powder for Solution for Infusion vial contains an excess fill of 10 mg (equivalent to 0.4 mL of reconstituted solution) to ensure the recovery of label claim of 50 mg pembrolizumab (MK-3475) per vial (equivalent to 2 mL of reconstituted solution).

3.2 STABILITY AND HANDLING OF DRUG PRODUCT

- Pembrolizumab (MK-3475) Powder for Solution for Infusion vials should be stored at refrigerated conditions 2 – 8 °C (36 - 46 ºF). Prior to reconstitution, the vial of lyophilized powder can be out of refrigeration (temperatures at or below 25°C (77°F)) for up to 24 hours.

- To determine whether to report a temperature excursion, the temperature values should be rounded to whole numbers.

  **Rounding:**
  1. Decimal values from 0.1 to 0.4 round down to the nearest whole number (e.g., 8.3 = 8)
  2. Decimal values from 0.5 to 0.9 round up to the nearest whole number (e.g., 8.7 = 9)

- Then compare the rounded values to the required temperature range to determine if there’s an excursion.
• All temperature excursions, however small, must be reported by the site to the Clinical Complaint Intake mailbox (clinical.complaints.intake@merck.com) for investigation within 1 business day using the Clinical Supply Complaint & GCP Inquiry Form (excel version) and attached temperature data. Please also notify your CRA or uCRA in trials with unblinded component. All Clinical Supply stock that is subject to an investigation must be placed in quarantine and remain unavailable to dispense to patients until disposition has been determined.

• Please note temperature excursions after drug product is prepared are out of scope of the clinical complaint process. Please contact HQ clinical study team for further guidance.

• Following reconstitution with sterile water for injection, Pembrolizumab (MK-3475) infusion solutions should be prepared in 0.9% Sodium Chloride Injection, USP (normal saline) or regional equivalent and the final concentration of pembrolizumab (MK-3475) in the infusion solutions should be between 1 mg/mL and 10 mg/mL.

• If normal saline is not available, 5% Dextrose Injection, USP or regional equivalent (5% dextrose) is permissible, Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

• Local guidelines should be followed for collection of diluent information such as manufacturer, lot and expiry. When the diluent is provided by Merck, the drug accountability log should be used for collection of diluent information.

• Pembrolizumab (MK-3475) SHOULDN’T BE MIXED WITH OTHER DILUENTS

• Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. The 6 hour countdown begins when the vial is pierced, and includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion. (Please note this 6 hour timeframe is to provide a microbial control strategy. The microbial clock only starts when the product stopper is pierced and not when the vial is removed from the refrigerator.)

• In addition, reconstituted vials and/or IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.
• If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

• Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if visible particles are observed.

• Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the reconstituted and diluted drug product between the pharmacy and the clinic

• **DO NOT USE PEMBROLIZUMAB (MK-3475) IF DISCOLORATION IS OBSERVED.**

• **DO NOT SHAKE OR FREEZE THE VIAL(S).**

• **DO NOT ADMINISTER THE PRODUCT AS AN INTRAVENOUS (IV) PUSH OR BOLUS.**

• **DO NOT COMBINE, DILUTE OR ADMINISTER IT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.**

• **DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.**

• Any departure from the guidance listed in this manual, must be discussed with sponsor

3.3 DOSE CALCULATION

*Retain only those dose calculations that are appropriate for your protocol. Delete the others.*

Follow directions applicable to the dose level (mg/kg) of the study

2 mg/kg Dose

• The preparation of infusion solutions should be based on the dose level and the subject’s actual body weight in kilograms (kg) on the day of dosing. However if preparation of the infusion is required to be completed prior to the subject’s visit
(e.g., per local SOP, logistical issues, etc.), then the solution may be prepared in advance in accordance with the instructions in this manual.

- If infusion solution is prepared in advance, weight from the most recent scheduled or unscheduled visit should be used.

- If the weight from the most recent scheduled or unscheduled visit is used, the dose amount should be recalculated and a new preparation of the infusion solution created if the subject's weight on the day of dosing changes by more than 10% from the last weight measurement.
  
  o Ex: 100 kg. at previous visit but current visit is less than 90 kg. or greater than 110 kg. then recalculation of the dose and a new preparation of infusion solution is required

- Required dose amount (mg) = dose level (mg/kg) * subject weight (kg)

- Calculate the required number of pembrolizumab (MK-3475) vials by dividing the required dose amount (mg) by 50 (mg) and rounding to the next whole number.

**Example 1 (2 mg/kg dose)**

Dose level = 2 mg/kg, subject weight = 69 kg
Required dose amount (mg) = 2 mg/kg * 69 kg = 138 mg
Required number of pembrolizumab (MK-3475) vials = 138/50 = 2.76
Rounded to next whole number = 3 vials

**10 mg/kg Dose**

- The preparation of infusion solutions should be based on the dose level and the subject’s actual body weight in kilograms (kg) on the day of dosing. However if preparation of the infusion is required to be completed prior to the subject’s visit (e.g., per local SOP, logistical issues, etc.), then the solution may be prepared in advance in accordance with the instructions in this manual.

- If infusion solution is prepared in advance, weight from the most recent scheduled or unscheduled visit should be used.

- If the weight from the most recent scheduled or unscheduled visit is used, the dose amount should be recalculated and a new preparation of the infusion solution created if
the subject’s weight on the day of dosing changes by more than 10% from the last weight measurement.

- Ex: 100 kg. at previous visit but current visit is less 90 kg. or greater 110 kg. then recalculation of the dose and a new preparation of infusion solution is required

- Required dose amount (mg) = dose level (mg/kg) * subject weight (kg)

- Calculate the required number of pembrolizumab (MK-3475) vials by dividing the required dose amount (mg) by 50 (mg) and rounding to the next whole number.

**Example 2 (10 mg/kg dose)**
Dose level = 10 mg/kg, subject weight = 69 kg
Required dose amount (mg) = 10 mg/kg * 69 kg = 690 mg
Required number of pembrolizumab (MK-3475) vials = 690/50 = 13.8
Rounded to next whole number = 14 vials

- Preference is for sites to prepare study medication on day of infusion. For sites that must prepare dose in advance, weight from most recent scheduled or unscheduled visit can be used for advanced preparation. Then on day of dosing, reweigh subject for actual weight.
  - If the weight on day of dosing is within 10% of weight used for advanced dose calculation, you can proceed with dosing what was prepared during advanced preparations
  - If a patient’s weight on day of dosing has fluctuated by more than 10% compared to weight used for advanced study prep, then the dose should be recalculated using the new weight measurement.

**200 mg Fixed Dose**
- Required Number of vials = 4 vials (50 mg/vial)
- 8 mLs Total
3.4 RECONSTITUTION OF DRUG PRODUCT (POWDER FOR SOLUTION FOR INFUSION, 50 MG/VIAL)

- Aseptic technique must be strictly observed throughout the preparation procedure.

- Use of a biosafety cabinet is preferred since no anti-microbial preservative is present in the product; however, it is not mandatory unless specified by site standard operating procedure.

- Equilibrate required number of pembrolizumab (MK-3475) vials to room temperature.

- The preferred method of dose preparation is the volumetric method.

- Sponsor recommends reconstitution and administration of pembrolizumab (MK-3475) that follows the parameters in this manual, however if use of gravimetric preparation is mandatory due to local site procedures, the following requirements must be satisfied and documented:
  
  - Draw the required volume up to 2.0 mL (50 mg) of pembrolizumab from each vial
  - Limit the number of punctures of each vial to two (one for reconstitution, one for withdrawal)

- For gravimetric preparation method using density of reconstituted pembrolizumab solution, a value of 1.03 g/mL should be used

- For gravimetric preparation method using the total solid content information, the following information on the total solid and active contents per vial of pembrolizumab lyophilized product should be used:
  
  - Total calculated weight of pembrolizumab per vial = 60.0 mg
  - Total calculated weight of solids per vial (including pembrolizumab) = 232.2 mg

- Merck does not support methods of preparation of non-Merck agents beyond what is stated in the product literature. Sites should reference the SmPCs or packaging inserts for preparation instructions.
• Remove the cap from the seal. **Do not decrimp the vial.**

• Insert a needle through the stopper of the pembrolizumab (MK-3475) Powder for Solution for Infusion vial(s) to release vacuum (if any). Leave the needle inserted in the stopper. If local standard operating procedures (SOPs) prohibit leaving a needle inserted in the stopper, this step can be skipped.

• If the site procedures require use of spikes or other closed system transfer devices (CSTDs), please contact sponsor for approval.

• If one WFI bottle is used to reconstitute one pembrolizumab (MK-3475) vial: Attach a 3 mL syringe to a needle. Insert the needle through the stopper of the sterile water for injection (WFI) bottle. Draw excess of 2.3 mL of WFI in the syringe and remove the syringe-needle assembly from the vial.

• If one WFI bottle is used to reconstitute more than one pembrolizumab (MK-3475) vials: Insert a needle through the stopper of the sterile WFI bottle. Attach a 3 mL syringe to the needle inserted in the sterile WFI bottle and draw excess of 2.3 mL of WFI in the syringe. Carefully detach the syringe without removing the needle from the WFI bottle. Repeat the process to fill additional syringes while keeping the needle inserted in sterile WFI bottle to minimize particle shedding from stopper. Use a new sterile WFI bottle after filling approximately 10 syringes.

• Attach a new needle to the filled syringe (if applicable). Remove excess air and WFI from the syringe-needle assembly while ensuring that there is 2.3 mL WFI still remaining in it.

• Aseptically add 2.3 mL of sterile water for injection to yield a 25 mg/mL (pH 5.2-5.8) solution of pembrolizumab (MK-3475).

**Caution: To avoid foaming, ensure that water is delivered along the walls of the vial and not directly squirted on the lyophilized powder.**

• Remove the needle(s) from the stopper of pembrolizumab (MK-3475) vial.

• Slowly swirl the vial to allow reconstitution of the lyophilized powder. Allow up to 5 minutes for the bubbles to clear.
Caution: Do not shake the vials otherwise this may result in formation of foam. If foam is noticed in either vial or bag, the drug product will need to be discarded. A new preparation should be made, taking care not to shake or agitate the product.

3.5 PREPARATION OF INFUSION SOLUTION

- Aseptic technique must be strictly observed throughout the preparation procedure.
- Reconstitute the required number of vials to prepare the infusion solution.
- Choose a suitable infusion bag size so that the following conditions are met:
  - Concentration of pembrolizumab (MK-3475) is between 1 mg/mL and 10 mg/mL
  - The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity.
- Choose a suitable infusion bag material. The bag may be empty or it may contain normal saline. The following infusion bag materials are compatible with pembrolizumab (MK-3475):
  - PVC plasticized with DEHP
  - Non-PVC (polyolefin)
  - EVA
  - PE lined polyolefin
  *Contact Sponsor for materials not listed above
- Calculate the volume of pembrolizumab (MK-3475) and normal saline required to prepare the infusion (admixture) bag

  \[
  \text{Volume of reconstituted pembrolizumab (MK-3475) (mL)} = \frac{\text{required dose amount (mg)}}{25 \text{ (mg/mL)}}
  \]

  \[
  \text{Volume of normal saline = total infusion volume – volume of pembrolizumab (MK-3475) from above}
  \]
- If a bag pre-filled with normal saline is being used, remove the excess volume of normal saline using a sterile syringe (Polypropylene, latex-free) attached to a suitable needle. Keep in consideration the excess bag fill volume as well as the volume of reconstituted
pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution. This helps ensure that the concentration in the bag can be accurately calculated and falls within the acceptable range of 1 mg/mL to 10 mg/mL. If the site would like to proceed without removing excess saline they must ensure that the concentration of MK-3475 would still fall within acceptable range.

- If an empty bag is being used, withdraw the necessary volume of normal saline from another appropriate bag and inject into the empty bag. Keep in consideration the volume of reconstituted pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution.

- Withdraw the required volume of pembrolizumab (MK-3475) from the vial(s) (up to 2 mL from each vial) using a sterile syringe attached to a suitable needle. The vial(s) may need to be inverted to remove solution.

  Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

  **Note:** If it is necessary to use several vials, it is advisable to withdraw from several vials into a suitable size single use syringe using a new needle for each vial.

- Add the required pembrolizumab (MK-3475) (reconstituted solution) into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.

- If the infusion bag is excessively handled or shaken, particulates may form. If this occurs, discard the bag and create a new bag. Please contact your HQ clinical study team if particulates are noticed for further instructions. Be prepared to provide the following information:
  - IV bag manufacture, lot and expiry
  - Target volume of admixture solution in the IV bag (e.g. 100 mL, 200 mL etc.)
  - Amount of drug product (mL or mg) added to the bag
  - Drug product lot
  - Brief description of the nature of visible particles (color, shape, size, numbers etc.)

- **DO NOT FREEZE THE PEMBROLIZUMAB (MK-3475) INFUSION SOLUTION.**

- Discard any unused portion left in the vial as the product contains no preservative
3.6 ADMINISTRATION

- Pembrolizumab (MK-3475) infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

- The following infusion set materials are compatible with pembrolizumab (MK-3475):
  
  - PVC Infusion set that is plasticized using DEHP
  - PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
  - Polyethylene lined PVC infusion set
  - PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
  - Polyurethane set

  *Contact Sponsor for materials not listed above*

- A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line *(Note: the materials of the extension line and filter should be as mentioned above).*

- Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.

- Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.

- Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered through saline flushing.

- Document volume administered according to data entry guidelines.

*In case of infusion reactions, infusion rate may differ; refer to protocol for specific instructions.*

- Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes
• Maximum rate of infusion should not exceed 6.7 mL/min through a peripheral line or indwelling catheter.

_The following bullet regarding 250 mL is only applicable to weight based studies, fixed dose studies should remove this bullet:_

• However, when it is necessary to infuse a larger volume (i.e., 250 ml), the flow rate may go as high as 10 mL/min (maximum) in order to keep the infusion within the window as defined above.

• **DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.**

• **UNUSED INFUSION SOLUTION FOR INJECTION SHOULD NOT BE USED FOR ANOTHER INFUSION OF THE SAME SUBJECT OR DIFFERENT SUBJECT.**

### 3.7 RETURN AND DISCARDING OF PEMBROLIZUMAB (MK-3475) VIALS

• Unused pembrolizumab (MK-3475) Powder for Solution for Infusion or Solution for Infusion vial(s) shall be returned to the designated facility for destruction after CRA has performed full accountability of un-used vials.

  o For US clinical sites, return to the central depot that shipped supplies to the site:
    ▪ Fisher Clinical Services, Return and Destruction Center, 700B Nestle Way, Breinigsville, PA 18031
    ▪ Merck & Co., Inc. 770 Sumneytown Pike B-78A West Point, PA 19486

  o For ex-US clinical sites, consult with local Merck subsidiary for facility address.

  o For clinical sites that are not able to return to designated facility for destruction, please work with your CRA and refer to SOP 104_ER5_Return and Destruction of Clinical Supplies Procedure for guidance to follow for destruction of unused vials at the local site.
For Interactive response technology (IRT) studies, the IRT Clinical Drug Supply Return Forms generated in the system must be used.

Solution remaining in a used vial should be discarded according to your local procedures.

Any information on the label identifying the subject should be redacted prior to returning the study medication.
Retain Section 4 if study is utilizing pembrolizumab (MK-3475) liquid formulation for infusion (e.g., Materials C or C’); otherwise delete all of Section 4.

4. Drug Preparation – Pembrolizumab (MK-3475) Solution for Infusion

4.1 DRUG PRODUCT

Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/4 mL vial

- Pembrolizumab (MK-3475) Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab (MK-3475). The product is preservative-free, latex free solution which is essentially free of extraneous particulates.

- Cap color of MK-3475 (Pembrolizumab) 100 mg vials:
  - Both red, salmon, and blue color caps may be used. Though the cap color may be different, the product inside the vial is the same MK-3475 drug product.

  - Pembrolizumab (MK-3475) Solution for Infusion vials are filled to a target of 4.25mL (106.25mg) to ensure recovery of 4.0mL (100mg).

4.2 STABILITY AND HANDLING OF DRUG PRODUCT

- Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/4 mL vial: pembrolizumab (MK-3475) Solution for Infusion vials should be stored at refrigerated conditions 2 – 8 °C (36 – 46 °F) and protected from light.

- To determine whether to report a temperature excursion, the temperature values should be rounded to whole numbers.
• **Rounding:**
  - Decimal values from 0.1 to 0.4 round down to the nearest whole number (e.g., 8.3 = 8)
  - Decimal values from 0.5 to 0.9 round up to the nearest whole number (e.g., 8.7 = 9)

• Then compare the rounded values to the required temperature range to determine if there's an excursion.

• All temperature excursions, however small, must be reported by the site to the Clinical Complaint Intake mailbox (clinical.complaints.intake@merck.com) for investigation within 1 business day using the Clinical Supply Complaint & GCP Inquiry Form (excel version) and attached temperature data. Please also notify your CRA or uCRA in trials with unblinded component. All Clinical Supply stock that is subject to an investigation must be placed in quarantine and remain unavailable to dispense to patients until disposition has been determined.

• Please note temperature excursions after drug product is prepared are out of scope of the clinical complaint process. Please contact HQ clinical study team for further guidance.

  **Note:** vials should be stored in the original box to ensure the drug product is protected from light.

• Pembrolizumab (MK-3475) infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent or **5% Dextrose Injection, USP** (5% dextrose) or regional equivalent and the final concentration of pembrolizumab (MK-3475) in the infusion solutions should be between 1 mg/mL and 10 mg/mL.

• Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

• Local guidelines should be followed for collection of diluent information such as manufacturer, lot and expiry. When the diluent is provided by Merck, the drug accountability log should be used for collection of diluent information.

• **Pembrolizumab (MK-3475) SHOULD NOT BE MIXED WITH OTHER DILUENTS.**

• Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. The 6 hour countdown begins when the vial is pierced, and includes room temperature storage of admixture solutions in the IV bags.
and the duration of infusion. (Please note this 6 hour timeframe is to provide a microbial control strategy. The microbial clock only starts when the product stopper is pierced and not when the vial is removed from the refrigerator.)

- In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.

- If refrigerated, allow the IV bags to come to room temperature prior to use.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if visible particles are observed.

- Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the drug product between the pharmacy and the clinic

- **DO NOT USE PEMBROLIZUMAB (MK-3475) IF DISCOLORATION IS OBSERVED.**

- **DO NOT SHAKE OR FREEZE THE VIAL(S).**

- **DO NOT ADMINISTER THE PRODUCT AS AN INTRAVENOUS (IV) PUSH OR BOLUS.**

- **DO NOT COMBINE, DILUTE OR ADMINISTER IT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.**

- Any departure from the guidance listed in this manual, must be discussed with sponsor

### 4.3 DOSE CALCULATION

Follow directions applicable to the dose level (mg/kg) of the study.

*Retain only those dose calculations that are appropriate for your protocol. Delete the others.*

#### 2 mg/kg Dose
• The preparation of infusion solutions should be based on the dose level and the subject’s actual body weight in kilograms (kg) on the day of dosing. However if preparation of the infusion is required to be completed prior to the subject’s visit (e.g., per local SOP, logistical issues, etc.), then the solution may be prepared in advance in accordance with the instructions in this manual.

• If infusion solution is prepared in advance, weight from the most recent scheduled or unscheduled visit should be used.

• If the weight from the most recent scheduled or unscheduled visit is used, the dose amount should be recalculated and a new preparation of the infusion solution created if the subject's weight on the day of dosing changes by more than 10% from the last weight measurement.
  
  o Ex: 100 kg at previous visit but current visit is less than 90 kg or greater than 110 kg, then re-calculation of the dose and a new preparation of infusion solution is required.

• Required dose amount (mg) = dose level (mg/kg) * subject weight (kg)

• Calculate the required number of pembrolizumab (MK-3475) vials by dividing the required dose amount (mg) by 100 (mg).

  **Example 1 (2 mg/kg dose):**
  Dose level = 2 mg/kg, subject weight = 69 kg
  Required dose amount (mg) = 2 mg/kg * 69 kg = 138 mg
  Required number of pembrolizumab (MK-3475) vials = 138/100 = 1.38
  Rounded to next whole number = 2 vials

**10 mg/kg Dose**

• The preparation of infusion solutions should be based on the dose level and the subject’s actual body weight in kilograms (kg) on the day of dosing. However if preparation of the infusion is required to be completed prior to the subject’s visit (e.g., per local SOP, logistical issues, etc.), then the solution may be prepared in advance in accordance with the instructions in this manual.

• If infusion solution is prepared in advance, weight from the most recent scheduled or unscheduled visit should be used.
• If the weight from the most recent scheduled or unscheduled visit is used, the dose amount should be recalculated and a new preparation of the infusion solution created if the subject's weight on the day of dosing changes by more than 10% from the last weight measurement.
  
  o Ex: 100 kg at previous visit but current visit is less than 90 kg or greater than 110 kg, then recalculation of the dose and a new preparation of infusion solution is required.

• Required dose amount (mg) = dose level (mg/kg) * subject weight (kg)

• Calculate the required number of pembrolizumab MK-3475 vials by dividing the required dose amount (mg) by 100 (mg).

Example 2 (10 mg/kg dose):
Dose level = 10 mg/kg, subject weight = 69 kg
Required dose amount (mg) = 10 mg/kg * 69 kg = 690 mg
Required number of pembrolizumab (MK-3475) vials = 690/100 = 6.9
Rounded to next whole number = 7 vials

• Preference is for sites to prepare study medication on day of infusion. For sites that must prepare dose in advance, weight from most recent scheduled or unscheduled visit can be used for advanced preparation. Then on day of dosing, reweigh subject for actual weight.
  
  ▪ If the weight on day of dosing is within 10% of weight used for advanced dose calculation, you can proceed with dosing what was prepared during advanced preparations
  
  ▪ If a patient’s weight on day of dosing has fluctuated by more than 10% compared to weight used for advanced study prep, then the dose should be recalculated using the new weight measurement.

200 mg Fixed Dose

• 2 vials (100 mg/4 mL)
• 8 mL total
4.4 PREPARATION OF INFUSION SOLUTION

- Aseptic technique must be strictly observed throughout the preparation procedure

- Use of a biosafety cabinet is preferred since no anti-microbial preservative is present in the product; however, it is not mandatory unless specified by site standard operating procedure.

- Equilibrate required number of pembrolizumab MK-3475 vials to room temperature

- The preferred method of dose preparation is the volumetric method

- Sponsor recommends reconstitution and administration of pembrolizumab (MK-3475) that follows the parameters in this manual, however if use of gravimetric preparation is mandatory due to local site procedures, the following requirements must be satisfied and documented:
  - Draw the required volume up to 4.0 mL (100 mg) of pembrolizumab from each vial
  - Limit the number of punctures of each vial to one

- For gravimetric preparation method using density of pembrolizumab solution, a value of 1.03 g/mL should be used

- Merck does not support methods of preparation of non-Merck agents beyond what is stated in the product literature. Sites should reference the SmPCs or packaging inserts for preparation instructions

- If the site procedures require use of spikes or other closed system transfer devices (CSTDs), please contact sponsor for approval

- Choose a suitable infusion bag size so that the following conditions are met:
  - Concentration of pembrolizumab MK-3475 is between 1 mg/mL and 10 mg/mL
  - The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity.

- Choose a suitable infusion bag material. The bag may be empty or it may contain normal saline. The following infusion bag materials are compatible with pembrolizumab (MK-3475):

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- PVC plasticized with DEHP
- Non-PVC (polyolefin)
- EVA
- PE lined polyolefin

*Contact Sponsor for materials not listed above

- Calculate the volume of pembrolizumab (MK-3475) and normal saline required to prepare the infusion (admixture) bag

Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

Volume of normal saline = total infusion volume – volume of pembrolizumab (MK-3475) from above

- If a bag pre-filled with normal saline is being used, remove the excess volume of normal saline using a sterile syringe (Polypropylene, latex-free) attached to a suitable needle. Keep in consideration the excess bag fill volume as well as the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution. This helps ensure that the concentration in the bag can be accurately calculated and falls within the acceptable range of 1 mg/mL to 10 mg/mL. If the site would like to proceed without removing excess saline they must ensure that the concentration of MK-3475 would still fall within acceptable range.

- If an empty bag is being used, withdraw the necessary volume of normal saline from another appropriate bag and inject into the empty bag. Keep in consideration the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution.

- Withdraw the required volume of pembrolizumab (MK-3475) from the vial(s) (up to 4 mL from each vial) using a sterile syringe attached to a suitable needle. The vial(s) may need to be inverted to remove solution.

Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

**Note:** If it is necessary to use several vials, it is advisable to withdraw from several vials into a suitable size single use syringe using a new needle for each vial.
• Add the required pembrolizumab (MK-3475) into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.

• Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion.

• In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.

• If refrigerated, allow the IV bags to come to room temperature prior to use.

• If the infusion bag is excessively handled or shaken, particulates may form. If this occurs discard the bag and create a new bag taking care not to shake. Please contact your HQ clinical study team if particulates are noticed for further instructions. Be prepared to provide the following information:
  • IV bag manufacture, lot and expiry
  • Target volume of admixture solution in the IV bag (e.g. 100 mL, 200 mL etc.)
  • Amount of drug product (mL or mg) added to the bag
  • Drug product lot
  • Brief description of the nature of visible particles (color, shape, size, numbers etc.).

• **DO NOT FREEZE THE PEMBROLIZUMAB (MK-3475) INFUSION SOLUTION.**

• Discard any unused portion left in the vial as the product contains no preservative

### 4.5 ADMINISTRATION

• Pembrolizumab (MK-3475) infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

• The following infusion set materials are compatible with (pembrolizumab) MK-3475:
  
  o PVC Infusion set that is plasticized using DEHP

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- PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
- Polyethylene lined PVC infusion set
- PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
- Polyurethane set

*Contact Sponsor for materials not listed above

- A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line (Note: the materials of the extension line and filter should be as mentioned above).

- Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.

- Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.

- Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered through saline flushing.

- Document volume administered according to data entry guidelines.

- *In case of infusion reactions, infusion rate may differ; refer to protocol for specific instructions.*

- Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes.

  *The following bullet regarding 250 mL is only applicable to weight based studies, fixed dose studies should remove this bullet:*

- Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter.

- However, when it is necessary to infuse a larger volume (i.e. 250 mL), the flow rate may go as high as 10 mL/min (maximum) in order to keep the infusion within the window as defined above.
• **DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.**

• **UNUSED INFUSION SOLUTION FOR INJECTION SHOULD NOT BE USED FOR ANOTHER INFUSION OF THE SAME SUBJECT OR DIFFERENT SUBJECT.**

• Caution: Do not shake the vials/bags otherwise this may result in formation of foam. If foam is noticed in either vial or bag, the drug product will need to be discarded. A new preparation should be made, taking care not to shake or agitate the product.

4.6 RETURN AND DISCARDING OF PEMBROLIZUMAB (MK-3475) VIALS

• Unused pembrolizumab (MK-3475) Solution for Infusion vial(s) shall be returned to the designated facility for destruction after CRA has performed full accountability of un-used vials
  
  o For US clinical sites, return to the central depot that shipped supplies to the site:
    ▪ Fisher Clinical Services, Return and Destruction Center, 700B Nestle Way, Breinigsville, PA 18031
    ▪ Merck & Co., Inc. 770 Sumneytown Pike B-78A West Point, PA 19486
  
  o For ex-US clinical sites, consult with local Merck subsidiary for facility address.

  o For clinical sites that are not able to return to designated facility for destruction, please work with your CRA and refer to SOP 104_ER5_Return and Destruction of Clinical Supplies Procedure for guidance to follow for destruction of unused vials at the local site.

• For Interactive response technology (IRT) studies, the IRT Clinical Drug Supply Return Forms generated in the system must be used

• Solution remaining in a used vial should be discarded according to your local procedures.
• Any information on the label identifying the subject should be redacted prior to returning the study medication.