- An MPO shall be prepared for each product, package size and type by Qualified personnel and approved by the Site Production Team and Site Quality Team.

- Each MPO shall:

  - Contain a unitized component list [e.g., Bill of Materials (BOM)];
  - Specify package size and type; and
  - Specify the acceptable ranges (expressed as percentages) of Actual Yields and Accountabilities.

- Each MPO must be complete, accurate, and describe in a logical order the sequence of activities necessary to fill, Label and package the product.

- MPOs and PBOs shall be maintained under change control according to the Site Standard Operating Procedures (SOP).

- MPOs shall be maintained under document management to ensure that only one approved master exists for each product, package size, and type for each standard lot size at a time.

- A PBO shall be prepared for each packaging lot and shall specify the Batch or lot size. Each PBO shall be Verified by a qualified person to be an accurate reproduction of the MPO.

  For validated systems that make reproductions of the MPO, this verification by a qualified person is not necessary, as it is covered by validation of the system. The verification can be replaced by a check on the legibility of the printout.

- Deviations from MPOs or PBOs shall be Investigated and documented.

- A System shall be established at each Site to retain MPOs and Batch Records (i.e., PBOs) according to site record retention requirements.

- Computerized Systems Used to Prepare MPOs and/or PBOs using Electronic Records and Electronic Signatures must be Validated.

- Each MPO must list or reference:
  - Stepwise filling, labelling, and/or packaging operations, including Process Parameters and Normal Operating Ranges (NOR);
  - Package size in terms of weight, number, or volume;
  - Product name, strength, dosage form, and reference code;
  - Definitions of all packaging/labelling materials needed, including quantities (unitized), sizes, types, and reference codes;
  - Major Equipment and packaging lines to be used;
  - SOPs or instructions for equipment or critical component preparation, cleaning, set-up, and operation, as required;
  - Statement of Theoretical Yields or accountabilities at key stages for product and printed Packaging Materials;

- Artwork Center Colleagues must receive a clear, legible and correct Editor's Copy from the market colleagues before they can proceed with the artwork changes.

For EC changes generated at a Site, the EC may be developed by the Site colleagues.

Minor production related changes to the artwork can be made without market colleagues' approval provided there is a written agreement from the market colleagues. Examples of minor production related changes may include the addition of relevant barcodes, color bars, or minor repositioning of copy for improved printability.

Changes to the EC generated at a Site must be clearly marked on the EC, initialed by the person making the change, and dated. Artwork Center colleagues must proofread such changes as part of the Artwork Center's responsibility.

- Artwork shall be created or revised electronically by Artwork colleagues based on the EC. Upon finalization, the electronic artwork shall be locked such that the artwork cannot be manipulated while it is in the review process. The output of the electronic artwork is generated from the locked file and compared to the EC.

  A procedure shall be available at each Artwork Center for assigning version numbers to the master labelling.

- Artwork Center Colleagues shall review the new or revised artwork against the EC to ensure:
  - There are no omissions or changes from the EC. This review may be performed either manually or using electronic systems; and
  - Artwork is graphically and technically correct.

- Artwork Center Colleagues must receive the signed copies of the final artwork from the responsible market colleagues indicating approval by a multi-disciplinary (e.g., Medical, Legal, Regulatory, Marketing, Quality) review of the artwork content.

  Electronic Signatures are allowed if the system is Validated and compliant with electronic signature and Electronic Record requirements.

- Master Labelling(s) shall be generated and maintained by the Artwork Center colleagues, after receipt of the artwork approval. The master labelling must match the artwork that was approved by the market colleagues as well as the result of any minor production related changes executed after market colleague approval.

  Master labelling may be hard copy output or electronic, if generated and housed within a validated system, which is compliant with electronic signature and electronic record requirements. The master labelling shall be sent to the

- Supplier name and Lot Number;
- Identity of the material, including site Label Revision Number;
- Individual quantity and number of containers received;
- Specimen of the inspected label or labelling;
- Packaging Material Lot Number and any site terminology, if different from suppliers;
- Name of manufacturer, if different from supplier, and manufacturer lot number; and
- Results of examination and any testing required to ensure conformance to specification.

- Storage of Labels and Labelling (including laser masks, rubber mats, and items related to labels and labelling that contain product information) shall include:
  - Storage in a continuously secure manner in a Limited Access Area or Restricted Access Area qualified personnel;
  - Restricted access areas shall be used to store individual container labels and API shipping container labels. Other labelling shall be stored in limited areas; and
  - Segregated storage by labelling lot number with proper identification provided for labels and labelling for each different product, strength, dosage form, quantity of contents, or other differentiating factors.

- Transport and Handling of Labels and Labelling, including laser masks, rubber mats, and related items with product information shall be performed in a manner designed to maintain the security and limited access to the labels and labelling, and shall include, and not be limited to:
  - Transport of printed labelling (e.g., roll labels, cut labels, preprinted glass cartridges) in properly identified, separate, and sealed containers;
  - Handling practices that maintain the unitized packaging of labelling (e.g., only a single preprinted lot number shrink-wrapped on a single pallet);
  - Prohibiting return of labels or labelling with lot codes or other batch-specific information to stock after completion of the Batch. Such items shall always be destroyed;
  - Segregation of labels and labelling that are assigned Reject or Quarantine-Hold status until disposed and
  - Segregation of outdated or obsolete labels until disposed.

Label and Labelling Issuance for Use in Production shall be strictly controlled and performed only by qualified personnel to other qualified personnel. The issuance and receipt of labels and labelling are recorded in the Packaging Batch Records.

- Each Laser Mask, Rubber Mat, and/or Related Items with Product, Lot/Batch, Manufacturing Date or Expiration Date Information must be verified against the Packaging Batch Order (PBO).

- Verification of Labels and Labelling Identification and Quantity shall be performed upon delivery to the packaging area and shall be recorded in the

- One hundred (100) percent electronic/electromechanical verification system; or
- One hundred (100) percent visual inspection with the examination performed by one person and independently verified by a second person. Electronic/electromechanical verification systems must be designed to reject the container or stop the labelling operation if a label cannot be positively verified (i.e. failsafe).

4. Container Closure Integrity for Sterile Drug Products

- The Suitability of All Container Closure Systems for Sterile Drug Products manufactured and/or packaged by the site shall be determined.

- The Effects of Environmental Stresses, Handling, and Simulated Use on Container Closure suitability shall be determined for new or changed container closure systems.

- The Container Closure Sealing Process for sterile drug products shall be Validated to ensure that the integrity of the container closure system will protect the product over its shelf life.

- Written and Approved Standard Operating Procedures (SOP) shall describe packaging/sealing equipment set-up, operation, and maintenance. Equipment and systems used in the sealing processes for packaging sterile drug products shall be qualified or validated.

- Validation Studies shall be conducted by Qualified personnel and shall be documented.
- Critical Process Parameters and Critical Process Parameter Ranges that affect container closure integrity shall be identified during the validation process for each container closure configuration.

- The Microbial Ingress Test shall be used to validate the integrity of the container closure system. The immersion method shall be used unless another method is justified (e.g., aerosol method).

- Non-Microbial Methods for Container Closure Integrity Testing [e.g., Residual Seal Force (RSF)] shall be used during routine production and shall be correlated to the microbial ingress test. In-Process Control (IPC) sampling for container closure integrity testing shall be representative of the packaged lot. Sampling and test procedures shall be written and approved.

- Action Levels and Specifications for Non-Microbial Methods for Container Closure Integrity Testing shall be established and validated for drug products sealed in glass vials having elastomeric closures.

- The Packaging System Sealing Process for sterile medical devices shall be Validated to ensure that the integrity of the package will protect the product over its shelf life.

- Written and Approved Standard Operating Procedures (SOP) shall describe packaging/sealing equipment set-up, operation, and maintenance. Equipment and systems used in the sealing processes for packaging sterile medical devices shall be Qualified or validated.

- Validation Studies shall be conducted by Qualified personnel and shall be documented.

- Critical Process Parameters and Critical Process Parameter Ranges that affect the packaging system integrity shall be identified during the validation process for each package configuration. These critical parameters and ranges shall be defined and provided in an SOP, and shall be controlled and monitored.

- In-Process Controls (IPC) sampling and testing procedures for verifying packaging system integrity shall be written and approved. IPC sampling for packaging system integrity testing shall be representative of the packaged lot.

- The Final Sterile Medical Devices Packaging System shall be evaluated or tested to validate the integrity of the packaging system, using one of the following methods:
  - Visual inspection;
  - Microbial barrier properties testing;
  - Seal/closure evaluation; or
  - Physical testing.

- Seal Integrity shall be sufficient to demonstrate that the seal is impermeable and continuous by using physical tests. Physical or non-microbial methods for packaging system integrity testing shall be used during routine production. Such physical testing together with microbial barrier property testing of materials establish the sterile packaging system integrity.

- The Microbial Barrier Properties of Packaging Materials shall be evaluated using one of the following two methods:
  - Methods for impermeable materials; or
  - Methods for porous materials.

- The Microbial Challenge Method used to determine the microbial barrier properties of the packaging material must be validated, according to an established Protocol, to demonstrate:
  - Acceptable Repeatability of the method; and
  - The ability to differentiate among packaging materials, examples of which are described in pharmacopoeias.

- If the Final Medical Device Package is not Closed by Sealing (e.g., Sterilization wraps, packaging for sterile fluid path products, reusable

