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# Objective

The objective of this document is to identify the control strategy for mixing and packaging process parameters for Gelnique™ (Oxybutynin Chloride) Gel 10%. The control strategy also addresses the controls in place to limit AQL defects in the finished drug product.

# Scope

This report covers Gelnique™ (Oxybutynin Chloride) Gel 10% bulk gel and finished product sachet packaging configurations manufactured at Actavis Laboratories UT, Inc.:

* Intermediate Bulk Gel
  + Item # 175547 – Oxybutynin Chloride Gel, 100 mg/g
* Finished Drug Product
  + Item 52544008430 – Gelnique Oxybutynin Chloride Gel, 10%, Ctn x 30 (US)
  + Item 52544008477 – Gelnique Oxybutynin Chloride Gel, 10%, Ctn x 7 (Sample, US)
  + Item 74028708430 – Gelnique Oxybutynin Chloride Gel, 10%, Carton x 30 (Canada)
  + Item 74028708477 – Gelnique Oxybutynin Chloride Gel, 10%, Carton x 7, Sample (Canada)

# Definitions

* **Critical Quality Attribute (CQA):**

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

* **Critical Process Parameter (CPP):**

A process parameter that is known to affect a Critical Quality Attribute (CQA) and must be controlled within a predetermined criteria to ensure that an intermediate, drug product, or material will meet its quality specifications.

* **In-Process Controls (IPCs):**

Tools to maintain Critical Process Parameters (CPPs) within pre-established ranges for steps that require repetitive execution to produce product that meets its quality specifications.

* **Acceptable Quality Levels (AQLs):**

The acceptable quality level, also known as acceptance quality limit, are established sampling plans and procedures for inspection of specific product attributes. The AQL sampling plans include acceptance criteria based on the criticality of the product attribute.

* **Control Strategy:**

Planned set of controls, derived from current product and process understanding, which ensures process performance and product quality. The controls may include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls (IPCs), finished product specifications and test methods, and the frequency of control monitoring.

# Control Strategy

The control strategies for mixing and packaging process parameters are addressed in this section. Additionally, control strategies are in place to prevent the generation of a nonconformance and detect visual defects.

| **Table 1: Control Strategy of Critical Process Parameters for Mixing Process; Oxybutynin Chloride Gel, 100 mg/g**  **(Batch Record #: MPR-0505)** | | | | |
| --- | --- | --- | --- | --- |
| **Batch Record Step(s)** | **Process**  **Step(s)** | **Process Parameters** | **Rationale** | **In-Process Controls and Control Strategy** |
| **Addition of sodium hydroxide side phase into main phase** | | | | |
| Section C:  Step 4 – 6 | Addition of Purified Water | N/A | The purpose of this mixing step is solubilize sodium hydroxide in purified and set it aside until neutralization step (**step # 26**) of the gelling agent. The mixing must be sufficient to solubilize sodium hydroxide in purified.  The blade speeds and mix time ranges were proven effective through stage I and stage II validation (see **M-0014-07** and **M-0030-07**). All of the batches produced were smooth, well-dispersed gel, indicating effective gelling agent dispersion.  CQAs Affected   * None | * Routine balance calibration and daily balance spot checks. * Equipment blade speed gauges are routinely calibrated. * These process steps are executed by two operators and recorded in the batch record. * The pH and viscosity of the gel is evaluated through analytical testing of the bulk gel and the finished product. * The addition of excipients is confirmed to be within 1% of the target amount. * Production supervisor batch record review. * Quality assurance batch record review. * Excipient pharmacy kit batch record controls and batch record review |
| Addition of Sodium Hydroxide |
| Mixing of the Side Phase | Manual stirring |
| Section C:  Step 26 – 33 | Addition of Side Phase into Main Phase | Anchor Blade:  21 RPM (17 – 24 RPM)  Disperser Blade:  965 RPM (950 – 980 RPM)  Vacuum Pressure:  20 in. Hg  Mixing Time:  120 mins (90 – 150 mins) |
| **Dissolution of the drug substance and excipients in the main phase** | | | | |
| Section C:  Step 15 | Addition of Alcohol Ethanol, USP | N/A | Component addition amounts directly affect the formula and in turn affect quality of the final product.  CQAs Affected   * Ethanol | * Routine balance calibration and daily balance spot checks. * This process step is executed by two operators and recorded in the batch record. * Production supervisor batch record review. * Quality assurance batch record review. * Active and excipient pharmacy kit batch record controls and batch record review * The addition of excipients is confirmed to be within 1% of the target amount. * The addition of drug substance is confirmed to be within 0.5% of the target amount. * The ethanol content and drug substance assay of the gel is evaluated through analytical testing of bulk and finished drug product. |
| Addition of Oxybutynin Chloride, USP |
| Addition of Glycerin USP / Glycerol EP |
| Section C: Step 17 – 19 | Mixing of drug substance and excipients in the main phase | Disperser Blade:  1245 RPM (1225 – 1260 RPM)  Mixing Time:  10 mins (5 – 15 mins)  Temperature:  59 – 95°F (15 – 35°C) | The purpose of this step is to form a solution prior to the addition of the gelling agent. The components are completely soluble or miscible.  The blade speeds and mix time ranges were proven effective through stage I and stage II validation (see **M-0014-07** and **M-0030-07**). All of the batches produced were smooth, well-dispersed gel, indicating effective gelling agent dispersion.  CQAs Affected   * Ethanol | * Equipment blade speed gauges are routinely calibrated. * Equipment temperature probe is routinely calibrated. * Batch record specifies mixing time and mix time range. * Production supervisor batch record review. * Quality assurance batch record review. * These process steps are executed by two operators and recorded in the batch record. |
| Section C:  Step 20 – 21 | Addition of Hydroxypropyl Cellulose, NF | Addition Time:  5 – 20 mins | The purpose of this step is to add gelling agent slowly in the main phase. Slow addition of the gelling agent promotes proper dispersion of the excipient in the main phase.  CQAs Affected  None | * Routine balance calibration and daily balance spot checks. * These process steps are executed by two operators and recorded in the batch record. * Production supervisor batch record review. * Quality assurance batch record review. * Active and excipient pharmacy kit batch record controls and batch record review * The addition of excipients is confirmed to be within 1% of the target amount. * Viscosity of the gel is evaluated through analytical testing of the bulk and finished drug product. |
| Section C:  Step 22 – 23 | Mixing of Hydroxypropyl Cellulose, NF | Anchor Blade:  21 RPM (17 – 24 RPM)  Disperser Blade:  1245 RPM (1225 – 1260 RPM)  Mixing Time:  60 mins (60 – 75 mins) | The mix composition is non-aqueous when the gelling agent is added so agglomeration is not an issue. This purpose of this step is to adequately disperse the gelling agent prior to the addition of water (in the form of a dilute NaOH solution). Incomplete dispersion prior to the addition of water could result in gelling agent agglomerations. Agglomeration increases the time required to fully solvate the gelling agent. Grossly incomplete solvation of the gelling agent could impact the final gel appearance, consistency and viscosity.  The blade speeds and mix time ranges were proven effective through stage I and stage II validation (see **M-0014-07** and **M-0030-07**). All of the batches produced were smooth, well-dispersed gel, indicating effective gelling agent dispersion.  CQAs Affected  None | * Equipment blade speed gauges are routinely calibrated. * Batch record specifies mixing time and mix time range. * Production supervisor batch record review. * Quality assurance batch record review. * These process steps are executed by two operators and recorded in the batch record. |
| **Final Mixing** | | | | |
| Section C:  Step 34 – 37 | Final mixing of the main phase | Disperser Blade:  Off  Anchor Blade:  21 RPM (17 – 24 RPM)  Mixing Time:  30 mins (20 – 40 mins)  Vacuum Pressure:  0 in. Hg  Temperature:  59 – 95°F (15 – 35°C) | The purpose of this mixing step is to solvate and neutralize the gelling agent. The mixing must also be adequate to create a uniform homogenous mixture as the gel thickens.  The blade speeds and mix time ranges were proven effective through stage I and stage II validation (see **M-0014-07** and **M-0030-07**). All of the batches produced were smooth, well-dispersed gel, indicating effective gelling agent dispersion.  CQAs Affected   * Ethanol | * Equipment blade speed gauges are routinely calibrated. * Equipment temperature probe is routinely calibrated. * Batch record specifies mixing time and mix time range. * Production supervisor batch record review. * Quality assurance batch record review. * These process steps are executed by two operators and recorded in the batch record. |

| Table : Control Strategy of Critical Process Parameter for Packaging Process; Gelnique Oxybutynin Chloride Gel, 10% , Carton x 30  (Batch Record #: MPR-0508; US / MPR-0847; Canada) | | | | |
| --- | --- | --- | --- | --- |
| **Batch Record Step(s)** | | **Process**  **Step(s)** | **Process Parameters /**  **In-Process Controls** | **Rationale** | **In-Process Controls and Control Strategy** |
| **Packaging – Form/Fill/Seal** | | | | | |
| Section 5 and 9 | | Sachet Forming / Sealing Steps | Process Parameters:  Machine Speed: 55 CPM (50 – 60 CPM)  Nitrogen Pressure: Min. 30 PSIG  (40 PSIG suggested set point)  Heat Seal: 165°C (155 – 175°C)  In-Process Testing:  Frequency: 30 – 45 mins  (not to exceed 60 mins)  Burst Strength: NLT 30 lbs  Visual Inspection: Meets batch record requirements | Machine speed controls has a direct impact on the dwell time of sealing the pouch. Therefore, it may impact the seal integrity of the sachet.  Out of range heat seal temperature can affect the seal integrity of the pouch. Therefore, it may impact drug release specifications.  The packaging parameters were challenged and proven effective during stage II validation (see **M-1229**) of the finished drug product.  Note that drug product dispensing nozzle may sporadically start drooling. Nozzle drooling will cause the drug product to be present at the sealing area of the sachet, thus impacting container closure integrity of the sachet.  CQAs Affected   * Assay * Minimum Fill * Ethanol * Drug Release | * Equipment qualifications, scheduled calibrations, and preventative maintenance. * Batch record specifies target, upper and lower end of machine speed. * Machine speed CPP recorded during each IPT. * Batch record specifies target, upper and lower end of heat seal temperature. * Heat seal temperature CPP recorded during each IPT. * Leaking sachets are readily obvious to the operators during manufacturing. The operators are trained to stop the machine, evaluate the product impact, and replace the damaged nozzles * Production supervisor batch record review. * Quality assurance batch record review. |
| Section 5 and 9 | | Sachet Filling | Process Parameters:  Machine Speed: 55 CPM  (50 – 60 CPM)  Fill Weights: 1.03 g  (0.96 – 1.10 g)  In-Process Testing:  Frequency: 30 – 45 mins  (not to exceed 60 mins)   * Fill Weights:   Reject Over: ≥ 1.105 g  Adjust: 1.065 – 1.104 g  UCL: 1.064 g  Target: 1.030 g  LCL: 0.995 g  Adjust: 0.955 – 0.994 g  Reject Under: ≤ 0.954 g | Incorrect fill weights can affect the quality of finished drug product.  The filling parameters were challenged and proven effective during stage II validation (see **M-1229**) of the finished drug product.  CQAs Affected   * Minimum Fill | * Routine balance calibration and daily balance spot checks. * Equipment qualifications, scheduled calibrations, and preventative maintenance. * Batch record specifies target, upper and lower end of sachet fill weight. * Sachet Fill weight recorded during each IPT. * Fill weight variation is monitored and evaluated through analytical testing of the finished drug product. * Production supervisor batch record review. * Quality assurance batch record review. |

| Table : Sachet AQL Control Strategy for Gelnique™ (Oxybutynin Chloride) Gel 10% | | |
| --- | --- | --- |
| **AQL Criticality** | **AQL Defect Description** | **In-Process Controls and Control Strategy** |
| Critical  (0.015) | Incorrect, missing, or illegible character(s) of the lot number. | * Electronic print verification system * Print verification system challenged prior to each batch. * Print setup is verified by two operators; a printed pouch specimen is attached to the batch record. The specimen is inspected by Manufacturing Supervision prior the start of production. |
| Incorrect, missing, or illegible character(s) of the expiration date. |
| Incorrect, missing, or illegible character(s) of the product name. | * Artwork change control * Analytical testing of the pouch material artwork is verified prior to use. * The sachet material artwork has item-specific barcodes. The barcodes are electronically verified for each pouch produced. * Sachets are visually inspected during setup and every 30-45 minutes (not to exceed 60 mins) of manufacturing run time. Visual blemishes can also be noticed by operators on the end of the manufacturing line handling the product. * Analytical testing of finished product appearance. |
| Incorrect, missing, or illegible character(s) of the dosage strength. |
| Major-A  (0.15) | Not Applicable | * Not Applicable |
| Major-B  (0.65) | Missing or illegible printing on sachet other than product name, dosage, or serialized numbering / time/date stamp. | * Sachets are visually inspected during setup and every 30-45 minutes (not to exceed 60 mins) of manufacturing run time. Visual blemishes can also be noticed by operators on the end of the manufacturing line handling the product. * Splice sensors to trigger system rejects. * Gel on sachets is observable by the operators during the manual steps of the secondary packaging process. * Analytical testing of finished drug product. * Leaking sachets are readily obvious to the operators during manufacturing. The operators are trained to stop the machine, evaluate the product impact, and replace the damaged nozzles * Procedural and design control strategies implemented to address the causes of leaking sachets. |
| Splices in sachet. |
| Sachet leaks. |
| Empty sachet/gross under fill. |
| Inadequate sachet seal. |
| Minor  (2.5) | Smeared printing or ink on the sachet, still legible. Excludes serialized numbering / time/date stamp. | * Sachets are visually inspected during setup and every 30-45 minutes (not to exceed 60 mins) of manufacturing run time. * Equipment qualifications, scheduled calibrations, and preventative maintenance * Operators are trained to observe stated defects during manual loading of sachets into carton. * Analytical testing of finished drug product. |
| Sachet seal alignment. Misalignment of the printed/unprinted roll stock during filling, yielding a visible strip of silver color along the sachet edge >1/8 inch. |
| Ragged edge of sachet material. |
| Absence of both tear notches. |
| Seal width <1/8 inch. |
| External delamination of sachet material. |
| If batch is designated as a sample batch, the word SAMPLE is absent or illegible from the pouch. |

| Table : Carton AQL Control Strategy for Gelnique™ (Oxybutynin Chloride) Gel 10% | | |
| --- | --- | --- |
| **AQL Criticality** | **AQL Defect Description** | **In-Process Controls and Control Strategy** |
| Critical  (0.015) | Incorrect, missing, or illegible character(s) within the Lot number. | * Batch record requires verification of printer setup. * Electronic verification of printed information. * Carton specimen with printed lot and expiry attached to batch record and reviewed prior to production. |
| Incorrect, missing, or illegible character(s) within the expiration date. |
| Incorrect, missing, or illegible character(s) within the product name. | * Artwork change control * Verification of printed artwork as part of the component internal release testing. * Batch record requires verification of carton barcode and verification of barcode reader setup * Electronic verification of barcode number; the barcode number is specific to the artwork * Carton specimen attached to batch record and reviewed prior to production * Line clearance verification/sign-off |
| Incorrect PI or PPI. |
| Major-A  (0.4) | Missing PI or PPI. | * Cartons are manually closed. A missing insert is readily observed when the carton is manually closed. * Missing inserts are detected by the carton checkweigher. |
| Major-B  (1.0) | Carton missing one or more sachets | * The loading of the cartons is automated; deficient number of sachets would only occur if backfilled after sampling. * The incorrect number of sachets is detected by the carton checkweigher. |
| Minor  (6.5) | Smeared but legible printing (lot number/expiration date) on carton. | * The cartons are manually erected and loaded. Cartons with smeared print are segregated or rejected by the operators. * Electronic verification of printed information; system would reject the carton as it could not locate / read the printing. * Analytical testing of insert appearance prior to use. * AQL attribute testing of insert prior to use. * Cartons are manually erected and closed. Damaged inserts or carton can be observed and replaced. * Analytical testing of carton appearance prior to use. * AQL attribute testing of cartons prior to use. |
| Incorrect placement of lot number/expiration date on carton |
| Damaged during packaging |
| Damaged PI or PPI during packaging. |

# References

| **Document Type** | **Document Name** | **Document #** |
| --- | --- | --- |
| Manufacturing Production Record | 175547 Oxybutynin Chloride Gel, 100 mg/g | MPR-0505 |
| 52544008430 Gelnique Oxybutynin Chloride Gel, 10% , Ctn x 30 (US) | MPR-0508 |
| 74028708430 Gelnique Oxybutynin Chloride Gel, 10% , Ctn x 30 (Canada) | MPR-0847 |
| Material Specification | Oxybutynin Chloride Gel, 100 mg/g | 175547 |
| Gelnique Oxybutynin Chloride Gel, 10% , Ctn x 30 (US) | 52544008430 |
| Gelnique Oxybutynin Chloride Gel, 10% , Ctn x 30 (Canada) | 74028708430 |
| Sampling Plan | Sampling of Oxybutynin Chloride Gel | SP404 |
| Sampling of Finished Product Oxybutynin Chloride Gel Sachets | SP910 |
| Standard Operating Procedures | Ross PVM – 100 Mixer | SLCSOP 948M-0112 |
| Mediseal LA-160 Packaging Line | SLCSOP 946F-0124 |
| Quality Assurance Manufacturing Room Audits | SLCSOP 721-0109 |
| Commercial Facility Batch Record Processing | SLCSOP 730-0057 |
| Processing Approved Commercial Labeling | SLCSOP 730-0069 |
| Acceptable Quality Level Testing | SLCSOP 720-0210 |
| Digital Force Gauge Compression Tester | SLCSOP 946F-0125 |
| Manufacturing Validation | Range Finding / Manufacturing Capability Study for Oxybutynin Chloride Gel, 100 mg/g, Processed using 100-Gallon Mixer (Eq. # 01766) | M-0014-07 |
| Process Validation of Oxybutynin Chloride Gel 100mg/g, (Item 400132), Manufactured using 100-Gallon Mixer Eq. # 01766 | M-0030-07 |
| Performance Qualification of the Gelnique 10% (8709) Form/Fill/Seal Manufacturing Process using Alternate Sachet material Item 208371 | M-1229 |