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# Objective

The objective of this report is to identify and assess the risk of Gelnique™ (Oxybutynin Chloride) Gel 10% process and product-related hazards.

# 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 Material Attributes (CMAs):**

A physical, chemical, or microbiological property or characteristic of drug substances, excipients, and in-process materials known to affect a critical quality attribute.

* **Critical Quality Attributes (CQAs):**

A physical, chemical, or microbiological characteristic of a product that should be within an appropriate limit, range or distribution to ensure the desired product quality. CQAs should only include product attributes that have the potential to be altered by changes to process parameters or formulation variables and are directly related to the safety and efficacy of the product.

* **Detectability:**

The ability to discover or determine the existence, presence or fact of a hazard.

* **Failure Modes:**

The specific way in which a system, process, or product can fail.

* **Harm:**

Physical injury or damage to the health of people, or damage to property or the environment.

* **Hazard:**

Potential source of harm.

* **Likelihood of Occurrence:**

The probability of the event occurring, existing or being present.

* **Mitigation:**

Risk reduction actions that lessens the impact or consequence of an unwanted event.

* **Quality Risk Management:**

A systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product life cycle.

* **Remediation:**

Risk reduction actions that lessen the chances of an unwanted event from occurring.

* **Residual Risk:**

Risk remaining after risk controls have been taken.

* **Risk:**

The combination of the likelihood of occurrence of harm and the severity of that harm.

* **Risk Assessment:**

A comprehensive evaluation of the risk and its associated impact.

* **Severity:**

The consequences of the event occurring.

# Hazard Identification and Risk Assessment

The Gelnique™ (Oxybutynin Chloride) Gel 10% Sachet hazard identification process is conducted per SLCSOP 920G-0107 “Product Risk Assessment and Control Strategy” and SLCSOP 000-0180 “Quality Risk Management.”

This report identifies the potential hazards related to the manufacturing process variables and critical material attributes (CMAs). This report evaluates the relationship between these potential hazards and the critical quality attributes (CQAs) identified in the QTTP (see **Attachment 2**). The evaluation includes determination of likely failure modes.

## Definition of Risk Evaluation Levels

The risk evaluation levels and categorization of risk factors “Severity” and “Likelihood of Occurrence” are defined in SLCSOP 920G-0107. The risk categorization only considers severity and likelihood of occurrence. Detectability of the hazards is considered when prioritizing the risks during the PHA (see **Attachment 4**).

| Table 1: Risk Severity Rating [from SLCSOP 920G-0107] | | | | | |
| --- | --- | --- | --- | --- | --- |
| **SEVERITY OF HARM** | | | | | |
| **Type of Impact** | **Rank** | **Degree of Effect** | **Qualitative Criteria** | **AQL Defect Level** | **Definition** |
| Significant Safety, Primary Labeling | 10 | Catastrophic Health Hazard | A failure that can by itself cause (directly) death or a permanent disability to a patient or user. Also labeling whose absence/illegibility/incorrectness creates a critical compliance impact. | Critical (0.015) | *A defect that would result in hazardous or unsafe conditions for an individual using, maintaining, or depending upon the product.* |
| 9 | Critical Health Hazard | A failure that can contribute (indirectly) to a death, temporary significant disability or severe occupational illness in a patient or user. | Critical(a)  (0.04) |
| Modest Safety, Secondary Labeling | 8 | Moderate Health Hazard | A failure that can cause a moderate, reversible injury to a patient or user, but will not result in death. The injury may require treatment, but does not lead to significant disability or severe occupational illness in a patient or user. Product is either partially or completely ineffective. | Major A (0.4) |
| 7 | Marginal Health Hazard | A failure that can cause transient minor injury to a patient or user. The injury may require treatment but has no long-term life limiting consequences. Also, labeling whose absence/ illegibility/ incorrectness creates a marginal compliance impact. |
| Usability | 6 | Major Dissatisfaction | Major user dissatisfaction, product either partially or completely inoperable, but safe, with no resulting injury to patient. | Major B (1.0) | *A non-critical defect that is likely to result in failure or materially reduce the usability of a unit or product for its intended purpose.* |
| 5 | Moderate Dissatisfaction | Moderate user dissatisfaction, performance degraded, but product remains safe and operable. No patient injury. |
| 4 | Minor Dissatisfaction | Customer experiences some minor nuisance and becomes slightly annoyed. Minor effect on product performance. Non-vital fault always noticed. No patient injury. |
| Cosmetic / Convenience | 3 | Moderate Inconvenience | Customer not annoyed. Slight effect on product performance. Non-vital fault noticed most of the time. No patient injury. | Minor (6.5) | *A defect that is not likely to materially reduce the usability or operation of a unit or product for its intended purpose.* |
| 2 | Minor Inconvenience | Customer not annoyed. Very slight effect on product performance. Non-vital fault may not even be noticed. No patient injury. |
| 1 | None | No negative impact at all. |

| Table 2: Risk Likelihood of Occurrence Rating [from SLCSOP 920G-0107] | | |
| --- | --- | --- |
| LIKELIHOOD OF OCCURRENCE | | |
| Rank | Likelihood of Occurrence | Criteria |
| **8 - 10** | **High** | Hazard is likely or certain (e.g. every day) |
| **4 - 7** | **Medium** | Hazard is possible / plausible (e.g. more than once a year) |
| **1 - 3** | **Low** | Hazard is impossible or unlikely (e.g. once every 1 or more years) |

| Table 3: Risk Categorization (without considering detectability) [from SLCSOP 920G-0107] | | |
| --- | --- | --- |
| **Initial Risk** | **Risk Level** | **Action** |
| **≥ 30** | **Unacceptable** | Identify and implement controls to reduce the risk. |
| **7 - 29** | **Undesirable** | Evaluation must be performed to determine if risk may be lowered. |
| **1-6** | **Acceptable** | None Required |

# Risk Assessment of Critical Material Attributes

Critical Material Attributes (CMAs) are properties or characteristics of raw materials, APIs and excipients that impact product CQAs. The CMAs include any attribute of the raw material that could potentially impact the identity, potency, purity, safety, efficacy or usability of the finished product. The potential CMAs identified in Table 4 are assigned a reference number and are further risk assessed in the Hazard Identification, Table 7.

The “*Ref. #*” column provides reference numbers assigned to the CQA and their associated factor (CMA or critical process step). Similar CQA’s are grouped together where applicable. The references are grouped as follows:

1. Assay
2. Minimum Fill
3. Impurities and degradation product
4. Ethanol
5. Drug Release

| Table 4: Risk Assessment of Critical Material Attributes | | | | |
| --- | --- | --- | --- | --- |
| **Component** | **Component Function** | **Attribute** | **Critical** | **Justification** |
| Oxybutynin Chloride, USP  Item: 175037 | API | Appearance | No | The drug substance is fully dissolved in the main phase as part of the mix process, rendering any powder differences in the API indistinguishable in the final product. Therefore, physical characteristics that impact solubility are not CMAs. |
| Identity  (Tests include  USP Identification A and B) | Yes\* | Identity is important for product quality; however, the attribute can be effectively controlled by the master batch record controls and materials managements system.  \*For the reasons above this CMA will not be discussed in detail in subsequent risk assessment. |
| Loss on Drying | Yes\* | Extra volatiles contained in the material could affect the potency of final drug product.  \*This CMA attribute is controlled to an acceptable level and therefore this will not be discussed in detail in subsequent risk assessment. |
| Organic Impurities | Yes | Impurities can affect the related substances and therefore affect the quality of the final product.  CQAs Affected   * Impurities and Degradation Products *(Ref. # 3.1)* |
| Residual Solvent | No | Residual solvents are controlled as per USP <467> limits. Therefore, this material attribute will not impact the CQA of intermediate and finished drug product. |
| Assay | Yes | The assay of the material directly affects the potency of the finished gel.  CQAs Affected   * Assay *(Ref. # 1.1)* * Drug Release *(Ref. # 5.1)* |
| Residue on Ignition | No | Does not affect critical quality attributes of intermediate or finished product |
| Heavy Metals | Yes\* | Prolonged exposure to heavy metals can cause deleterious health effects in humans.  \*Heavy metals are adequately controlled by incoming raw material testing and therefore this will not be discussed in detail in subsequent risk assessment. |
| Chloride Content | No | Does not affect critical quality attributes of intermediate or finished drug product, |
| Purified Water, USP/EP  Item: Plant System | Solvent | Microbial Purity | Yes\* | The purity of the water can directly impact the safety of the finished drug product but is effectively monitored and controlled by Environmental Monitoring of the Commercial Manufacturing and Development Facilities procedure (SLCSOP 000-0094). In addition, the drug product is a hydro-alcoholic gel; therefore, formulation contains anti-microbial properties.  \*For the reasons above this CMA will not be discussed in detail in subsequent risk assessment. |
| Conductivity | Yes\* |
| Total Organic Content | Yes\* |
| Sodium Hydroxide, NF/EP  Item: 175025 | Buffering Agent | Appearance | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Identity  (Test Includes EP and NF Requirements) | Yes\* | Identity is important for product quality; however, the attribute can be effectively controlled by the master batch record controls and materials managements system.  \*For the reasons above this CMA will not be discussed in detail in subsequent risk assessment. |
| Potassium | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Insoluble Substances and Organic Matter | No |
| Heavy Metals | Yes\* | Prolonged exposure to heavy metals can cause deleterious health effects in humans.  \*Heavy metals are adequately controlled by incoming raw material testing and therefore this will not be discussed in detail in subsequent risk assessment. |
| Assay  (Includes EP and NF Requirements) | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Iron | No |
| Residual Solvent (NF requirement) | No |
| Chlorides | No |
| Sulphates | No |
| Carbonates (R) | No |
| Alcohol Ethanol, USP  Item: 175039 | Solvent | Appearance  (Includes Clarity of Solution and Color of Solution) | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Identity  (Tests include  USP Identification A and B) | Yes\* | Identity is important for product quality; however, the attribute can be effectively controlled by the master batch record controls and materials managements system.  \*For the reasons above this CMA will not be discussed in detail in subsequent risk assessment. |
| Specific Gravity | Yes\* | Directly related to the density of the finished product. However, density is not considered a CQA.  In addition, specific gravity is directly related to purity of ethanol. Therefore, variation in specific gravity will impact the assay of ethanol content. However, this attribute can be effectively controlled by the master batch record controls and materials management system.  \*For the reasons above this CMA will not be discussed in detail in subsequent risk assessment. |
| Acidity or Alkalinity | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Organic Impurities | No |
| Non-Volatile Residue | No |
| USP Ultraviolet Absorption (R) | No |
| Glycerin, USP / Glycerol, EP  Item: 175024 | Emollient | Appearance  (Tests include  USP and EP Requirements) | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Identity  (Tests include  USP and EP Requirements) | Yes\* | Identity is important for product quality; however, the attribute can be effectively controlled by the master batch record controls and materials managements system.  \*For the reasons above this CMA will not be discussed in detail in subsequent risk assessment. |
| Related Compounds  (Tests include  USP and EP Requirements) | No | Does not affect critical quality attributes of intermediate or finished drug product |
| Assay  (Tests include  USP and EP Requirements) | No |
| Acidity or Alkalinity | No |
| Refractive Index | No |
| Aldehydes | No |
| Halogenated Compounds | No |
| Sugars | No |
| Chlorides | No |
| Heavy Metals | No |
| Water | No |
| Sulphated Ash | No |
| Color | No |
| Specific Gravity | No |
| Residue on Ignition | No |
| Fatty Acids and Esters  (USP Requirement) | No |
| Esters  (EP Requirement) | No |
| Hydroxypropyl Cellulose, NF  Item: 175038 | Gelling Agent | Appearance | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Identity  (Tests include  NF Requirements) | Yes\* | Identity is important for product quality; however, the attribute can be effectively controlled by the master batch record controls and materials managements system.  \*For the reasons above this CMA will not be discussed in detail in subsequent risk assessment. |
| Residue on Ignition | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Heavy Metals | Yes\* | Prolonged exposure to heavy metals can cause deleterious health effects in humans.  \*Heavy metals are adequately controlled by incoming raw material testing and therefore this will not be discussed in detail in subsequent risk assessment. |
| pH | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Residual Solvent | No |
| Loss on Drying | No |
| Lead | No |
| Assay | No |
| Moles of Substitution  (Vendor Test) | Yes\* | Variability in these attributes will impact the viscosity of the finished drug product. However, these attributes are effectively monitored by material managements system and controlled by vendor specification.  \*For the reasons above these CMAs will not be discussed in detail in subsequent risk assessment |
| Hydroxypropoxy Groups, %  (Vendor Test) | Yes\* |
| 1% Visc. H2O (3@30), 25°C, cps  (Vendor Test) | Yes\* |
| Sachet Material  Item: 208371 (US) and 233173 (Canada) | Primary Packaging | Appearance | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Identity | Yes\* | Identity is important for product quality; however, the attribute can be effectively controlled by the master batch record controls and materials managements system.  \*For the reasons above this CMA will not be discussed in detail in subsequent risk assessment. |
| Label Text | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Print Color | No |
| Bar Code Scanning | No |
| Total Basis Weight | No |
| Resin Gels | Yes\* | The material’s ability to seal consistently is critical to the pouch material function; however, the attribute can be effectively controlled by testing before the material is released.  \*For the reasons above this CMA will not be discussed in detail in subsequent risk assessment. |
| Acceptable Quality Levels | Yes | Defects in the material including tears or holes in the material affect the quality and usability of the product. Foreign material could lead to contamination of the product. Illegible text affects the ability to identify the product.  CQAs Affected   * Drug Release *(Ref # 5.2)* |
| Carton (30 units)  Item: 198150 (US) and 227458 (Canada) | Secondary packaging | Appearance | No | Does not affect critical quality attributes of intermediate or finished drug product. |
| Label Text | No |
| Print Color | No |
| Bar Code Scanning | No |
| Functionality | No |
| Caliper | No |
| Dimensions | No |
| Unvarnished Area | No |
| Acceptable Quality Levels | No |

# Risk Assessment of Manufacturing Process Variables

In this section processing steps from the mix and packaging processes are assessed for potential impact to the potency, purity, safety, efficacy and usability of the intermediate and finished drug product. The associated hazards which have an effect on CQAs are addressed in further detail in the hazard risk evaluation section.

Since all raw materials readily dissolve in the product solvent, dissolution of raw material is not considered critical for process parameter. The order of addition of each raw material was determined and fixed during formulation and process development; see technical report titled “Oxybutynin Chloride Topical Gel Formulation Development / Technology Transfer Report “; Report # **TR-8709-27** for more details.

To investigate the manufacturing process of the drug product, the mixing and packaging process is divided into five (5) sub steps as shown below. Note that in the batch record each step can be further divided into several steps for better control over the manufacturing process.

1. Dissolution of the drug substance and excipients in the main phase
2. Addition of thickening agent in the main phase
3. Addition of sodium hydroxide side phase into main phase
4. Final Mixing
5. Packaging – Form/Fill/Seal

| Table 5: Risk Assessment of Manufacturing Process Variables | | | |
| --- | --- | --- | --- |
| **Unit Operation(s)** | **Process Variable** | **Critical** | **Justification** |
| Dissolution of the drug substance and excipients in the main phase | Disperser Mixer Speed | Yes | Thorough mixing within validated parameters ensures complete dissolution of the drug substance and homogeneity of ethanol in bulk drug product. This directly affects the quality of intermediate and finished drug product.  CQAs Affected   * Assay *(Ref. # 1.2)* * Ethanol *(Ref. # 4.1)* |
| Mixing Time | Yes | Thorough mixing within validated parameters ensures complete dissolution of the drug substance and homogeneity of ethanol in bulk drug product. This directly affects the quality of intermediate and finished drug product  CQAs Affected   * Assay *(Ref. # 1.3)* * Ethanol *(Ref. # 4.2)* |
| Temperature | No | Based on prior experience with similar drug product, this process variable does not affect the critical quality attributes of intermediate and finished drug product. |
| Addition of thickening agent in the main phase | Addition Time | No | These process variables were developed in range finding study (see **M-0014-07)** and included in stage II validation Phase (see **M-0030-07**). Based on the stage II validation phase report, these process variables were deemed critical to establish the manufacturing process but the range finding study indicated they do not impact the CQA’s of the drug product identified in this report (see **Attachment 2**). Therefore, these process variables will not be considered critical for on-going risk assessment.  \*For reasons listed above these CPP will not be discussed in detail in subsequent risk assessment. |
| Disperser Mixer Speed | Yes\* |
| Anchor Mixer Speed | Yes\* |
| Mixing Time | Yes\* |
| Addition of sodium hydroxide side phase into main phase | Disperser Mixer Speed | Yes\* | These process variables were developed in range finding study (see **M-0014-07)** and included in Stage 1Validation Phase (see **M-0030-07**). Based on the Stage 1 Validation phase report, these process variables were deemed critical to establish the manufacturing process but the range finding study indicated they do not impact the CQA’s of the drug product identified in this report (see **Attachment 2**). Therefore, these process variables will not be considered critical for on-going risk assessment.  \*For reasons listed above these CPP will not be discussed in detail in subsequent risk assessment. |
| Anchor Mixer Speed | Yes\* |
| Mixing Time | Yes\* |
| Vacuum Pressure | No | This process variable does not affect the critical quality attributes of intermediate and finished drug product. |
| Final Mixing | Anchor Mixer Speed | Yes | Thorough mixing within validated parameters ensures complete dissolution of the drug substance and homogeneity of ethanol in bulk drug product. This directly affects the quality of intermediate and finished drug product.  CQAs Affected   * Assay *(Ref. # 1.4)* * Ethanol *(Ref. # 4.3)* |
| Mixing Time | Yes | Thorough mixing within validated parameters ensures complete dissolution of the drug substance and homogeneity of ethanol in bulk drug product. This directly affects the quality of intermediate and finished drug product  CQAs Affected   * Assay *(Ref. # 1.5)* * Ethanol *(Ref. # 4.4)* |
| Temperature | No | Based on prior experience with similar drug product, this process variable does not affect the critical quality attributes of intermediate and finished drug product. |
| Disperser Mixer Speed | Yes | Thorough mixing within validated parameters ensures complete dissolution of the drug substance and homogeneity of ethanol in bulk drug product. This directly affects the quality of intermediate and finished drug product.  CQAs Affected   * Assay *(Ref. # 1.6)* * Ethanol  *(Ref. # 4.5)* |
| Vacuum Pressure | No | This process variable does not affect the critical quality attributes of intermediate and finished drug product. |
| Packaging – Form/Fill/Seal | Machine Speed | Yes | 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.  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 *(Ref. # 1.7)* * Ethanol *(Ref. # 4.6)* * Minimum Fill *(Ref. # 2.1)* * Drug Release *(Ref. # 5.3)* |
| Nitrogen Pressure | No | This process variable does not affect the critical quality attribute of intermediate and finished drug product. |
| Heat Seal | Yes | Out of range heat seal temperature can affect the seal integrity of the pouch. Therefore, it may impact drug release specifications.  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 *(Ref. # 1.8)* * Ethanol *(Ref. # 4.7)* * Minimum Fill *(Ref. # 2.2)* * Drug Release *(Ref. # 5.4)* |
| Fill Weight | Yes | Incorrect fill weights can affect the quality of finished drug product.  CQAs Affected   * Minimum Fill *(Ref. # 2.3)* |
| Visual Test for Lot and Expiry Printing on the Label | Yes\* | Ensuring the proper lot and expiration date are recorded on the sachet label is important product quality.  \*The label printing is effectively controlled by the master batch record controls, vision system check, and testing before the material is released and will not be discussed in detail in subsequent risk assessment. |
| Visual Test for Lot and Expiry Printing on the Carton | Yes\* | Ensuring the proper lot and expiration date are recorded on the carton is important product quality.  \*The carton printing is effectively controlled by the master batch record controls, the vision system, and testing before the material is released and will not be discussed in detail in subsequent risk assessment. |

# Hazard Risk Evaluation

The critical material attributes and critical process variables are discussed and identified in **Table 4** and **Table 5**. The hazard risk number for CMAs and process variables impacting CQAs is provided in the table below. Please note that these hazard risk numbers are used throughout PRACS attachments.

The likelihood of occurrence evaluation is based on the time period identified in PRACS **Attachment 6** titled “Statistically Based Risk Evaluation (SBRE)”. This period covers all lots manufactured using the updated sachet material (Item #: 208371 (US) and 233173 (Canada)) from 04/14/2015 to 11/09/2016.

| **Table 6: Lots Examined for Likelihood Analysis** | |
| --- | --- |
| **Manufacturing Process** | **Lots Numbers** |
| Intermediate | 1004878, 1010985, 1031564, 1083918, 1091470, 1109752, 1122242, 1148794, 1156299, 1161375 |
| Finished Drug Product  (US and Canada) | 1004880, 1015302, 1015305, 1040760, 1091471, 1099489, 1109753, 1145883, 1148797 |

| Table 7: Hazard Identification | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref. #** | **Affected CQA** | **Influencing CMAs/Critical Processing Variable** | **Severity** | **Occurrence** | **Risk Category** | **Risk Assessment Rationale** |
| 1.1 | Assay | Oxybutynin Chloride, USP –  Assay | **6** | **2** | **12**  **Undesirable** | **Severity:** The drug substance assay can directly affect the API content in the finished product. An out of specification assay percentage can result in an out of specification intermediate solution and/or finished drug product assay, thus resulting in a batch failure. This can influence the efficacy of the product and hence can be either partially or completely ineffective. It could potentially lead to an excessive or reduced dose of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied OHC 3 and OEL 10 µg/m3; it will not adversely impact patient safety.  **Occurrence:** Within the evaluation period there are no instances of raw material API OOS assay results impacting the assay of finished drug product. |
| 1.2 | Assay | Dissolution of the drug substance and excipients in the main phase (Intermediate) –  Disperser Mixer Speed | **6** | **1** | **6**  **Acceptable** | **Severity:** Running outside of the validated parameters could affect the dissolution of the DS, which could lead to OOS assay results. This can influence the efficacy of the product and hence can be either partially or completely ineffective. It could potentially lead to an excessive or reduced dose of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied, OHC 3 and OEL 10 µg/m3, it will not adversely impact patient safety.  **Occurrence:** Within the evaluation period there are no instances of mixer speed going out of validated range. |
| 1.3 | Assay | Dissolution of the drug substance and excipients in the main phase (Intermediate) –  Mixing Time | **6** | **1** | **6**  **Acceptable** | **Severity:** Running outside of the validated parameters could affect the dissolution of the DS, which could lead to OOS assay results. This can influence the efficacy of the product and hence can be either partially or completely ineffective. It could potentially lead to an excessive or reduced dose of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied, OHC 3 and OEL 10 µg/m3, it will not adversely impact patient safety.  **Occurrence:** Within the evaluation period there are no instances of mixing time going out of validated range. |
| 1.4 | Assay | Final Mixing (Intermediate) –  Anchor Mixer Speed | **6** | **1** | **6**  **Acceptable** | **Severity:** Running outside of the validated parameters could affect the dissolution of the DS, which could lead to OOS assay results. This can influence the efficacy of the product and hence can be either partially or completely ineffective. It could potentially lead to an excessive or reduced dose of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied, OHC 3 and OEL 10 µg/m3, it will not adversely impact patient safety.  **Occurrence:** Within the evaluation period there are no instances of mixer speed going out of validated range. |
| 1.5 | Assay | Final Mixing (Intermediate) –  Mixing Time | **6** | **1** | **6**  **Acceptable** | **Severity:** Running outside of the validated parameters could affect the dissolution of the DS, which could lead to OOS assay results. This can influence the efficacy of the product and hence can be either partially or completely ineffective. It could potentially lead to an excessive or reduced dose of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied, OHC 3 and OEL 10 µg/m3, it will not adversely impact patient safety.  **Occurrence:** Within the evaluation period there are no instances of mixing time going out of validated range. |
| 1.6 | Assay | Final Mixing (Intermediate) –  Disperser Mixer Speed | **6** | **1** | **6**  **Acceptable** | **Severity:** Running outside of the validated parameters could affect the dissolution of the DS, which could lead to OOS assay results. This can influence the efficacy of the product and hence can be either partially or completely ineffective. It could potentially lead to an excessive or reduced dose of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied, OHC 3 and OEL 10 µg/m3, it will not adversely impact patient safety.  **Occurrence:** Within the evaluation period there are no instances of mixer speed going out of validated range. |
| 1.7 | Assay | Packaging – Form/Fill/Seal –  Machine Speed | **6** | **3** | **18**  **Undesirable** | **Severity:** The dwell time of the heat seal is controlled by machine speed. Out of range machine speed may impact the container closure integrity of sachet. Poor seals can result in compromised container closure integrity which directly impacts the stability, purity and efficacy of the finished drug product. It could potentially lead to an excessive of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied, OHC 3 and OEL 10 µg/m3, it will not adversely impact patient safety.  In addition, 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.  **Occurrence:** Within the evaluation period there are no instances of OOS assay result for finished drug product. |
| 1.8 | Assay | Packaging – Form/Fill/Seal –  Heat Seal | **6** | **3** | **18**  **Undesirable** | **Severity:** Damaged, worn, or misaligned heat seal platens can result in poor heat seals. In addition, Incorrect heat seal temperatures can result in poor heat seals. Poor heat seals can result in compromised container closure integrity which directly impacts the stability, purity and efficacy of the finished drug product. It could potentially lead to an excessive of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied, OHC 3 and OEL 10 µg/m3, it will not adversely impact patient safety.  In addition, 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.  **Occurrence:** Within the evaluation period there are no instances of an OOS assay results for finished drug product. |
| 2.1 | Minimum Fill | Packaging – Form/Fill/Seal –  Machine Speed | **10** | **2** | **20**  **Undesirable** | **Severity:** The dwell time of the heat seal is controlled by machine speed. Out of range machine speed may impact the container closure integrity of sachet. In addition, 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.  These process variables may lead to a poor seal or illegible product information. Based on Risk Severity Rating (see **Table 1)** Incorrect, missing, or illegible product information is considered a compliance impact on finished drug product. It will not adversely impact patient safety.  **Occurrence:** Within the evaluation period there are no instances of OOS minimum fill value in the finished drug product. |
| 2.2 | Minimum Fill | Packaging – Form/Fill/Seal –  Heat Seal | **6** | **2** | **12**  **Undesirable** | **Severity:** Damaged, worn, or misaligned heat seal platens can result in poor heat seals. In addition, Incorrect heat seal temperatures can result in poor heat seals. Poor heat seals can result in compromised container closure integrity which directly impacts the stability, purity and efficacy of the finished drug product. It could potentially lead to an excessive of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied, OHC 3 and OEL 10 µg/m3, it will not adversely impact patient safety.  In addition, 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.  **Occurrence:** Within the evaluation period there are no instances of OOS minimum fill value in the finished drug product. |
| 2.3 | Minimum Fill | Packaging – Form/Fill/Seal –  Fill Weight | **6** | **2** | **12**  **Undesirable** | **Severity:** Fill weight variation can directly affect the drug substance assay value in the finished drug product. An out of specification fill weight can result in an out of specification finished drug product minimum fill, thus resulting in a batch failure. This can influence the efficacy and quality of the finished drug product and hence can be either partially or completely ineffective. It could potentially lead to an excessive or reduced dose of Oxybutynin Chloride, USP.  **Occurrence:** Within the evaluation period there are no instances of OOS minimum fill value in the finished drug product. |
| 3.1 | Impurities and Degradation Product | Oxybutynin Chloride, USP –  Organic Impurities | **6** | **1** | **6**  **Acceptable** | **Severity:** high organic impurities in the drug substance may directly affect the degradation products in the bulk and finished drug product. An out of specification result for organic impurities can result in an out of specification result in the finished product, thus resulting in a batch failure. This is not likely to influence the safety of the drug product but it will impact the efficacy of the drug product.  **Occurrence:** Within the evaluation period there are no instance of using DS with OOS impurities and degradation values in a commercial batch. |
| 4.1 | Ethanol | Dissolution of the drug substance and excipients in the main phase (Intermediate) –  Disperser Mixer Speed | **6** | **2** | **12**  **Undesirable** | **Severity:** Running outside of the validated parameters could affect the homogeneity of ethanol, which could lead to OOS ethanol content results. This can influence the efficacy and quality of the drug product.  **Occurrence:** Within the evaluation period there are no instances of an OOS ethanol results for intermediate and finished drug product. |
| 4.2 | Ethanol | Dissolution of the drug substance and excipients in the main phase (Intermediate) –  Mixing Time | **6** | **2** | **12**  **Undesirable** |
| 4.3 | Ethanol | Final Mixing (Intermediate) –  Anchor Mixer Speed | **6** | **2** | **12**  **Undesirable** |
| 4.4 | Ethanol | Final Mixing (Intermediate) –  Mixing Time | **6** | **2** | **12**  **Undesirable** |
| 4.5 | Ethanol | Final Mixing (Intermediate) –  Disperser Mixer Speed | **6** | **2** | **12**  **Undesirable** |
| 4.6 | Ethanol | Packaging – Form/Fill/Seal –  Machine Speed | **6** | **3** | **18**  **Undesirable** | **Severity:** The dwell time of the heat seal is controlled by machine speed. Out of range machine speed may impact the container closure integrity of sachet. Poor seals can result in compromised container closure integrity which directly impacts the stability, purity and efficacy of the finished drug product.  In addition, it could lead to evaporation of volatile components (ethanol and water) of formulation from finished drug product. Ethanol functions as a skin permeation enhancer. Therefore, reduced amount of ethanol content impacts the efficacy 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.  **Occurrence:** Within the evaluation period there are no instances of OOS ethanol content for finished drug product. |
| 4.7 | Ethanol | Packaging – Form/Fill/Seal –  Heat Seal | **6** | **3** | **18**  **Undesirable** | **Severity:** Damaged, worn, or misaligned heat seal platens can result in poor heat seals. In addition, Incorrect heat seal temperatures can result in poor heat seals. Poor seals can result in compromised container closure integrity which directly impacts the stability, purity and efficacy of the finished drug product.  In addition, it could lead to evaporation of volatile components (ethanol and water) of formulation from finished drug product. Ethanol functions as a skin permeation enhancer. Therefore, reduced amount of ethanol content impacts the efficacy 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.  **Occurrence:** Within the evaluation period there are no instances of OOS ethanol content for finished drug product. |
| 5.1 | Drug Release | Oxybutynin Chloride, USP –  Assay | **6** | **2** | **12**  **Undesirable** | **Severity:** The drug substance can directly affect the API content in the finished product. An out of specification assay percentage can result in an out of specification intermediate solution and/or finished drug product assay, thus resulting in a batch failure. This can influence the efficacy of the product and hence can be either partially or completely ineffective. It could potentially lead to an excessive or reduced dose of Oxybutynin Chloride, USP  **Occurrence:** Within the evaluation period there are no instances of raw material API OOS assay results impacting the assay of finished drug product. |
| 5.2 | Drug Release | Sachet Material –  AQL | **10** | **2** | **20**  **Undesirable** | **Severity:** The sachet material is pre-printed with the product description and dosage. Based on Risk Severity Rating (see **Table 1**) Incorrect, missing, or illegible product information is considered a compliance impact on finished drug product. It will not adversely impact patient safety.  **Occurrence:** Within the evaluation period there are no instances of an OOS results for finished drug product. |
| 5.3 | Drug Release | Packaging – Form/Fill/Seal –  Machine Speed | **10** | **2** | **20**  **Undesirable** | **Severity:** The dwell time of the heat seal is controlled by machine speed. Out of range machine speed may impact the container closure integrity of sachet. In addition, 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.  These process variables may lead to a poor seal or illegible product information. Based on Risk Severity Rating (see **Table 1)** Incorrect, missing, or illegible product information is considered a compliance impact on finished drug product. It will not adversely impact patient safety.  **Occurrence:** Within the evaluation period there are no instances of an OOS drug release results for finished drug product. |
| 5.4 | Drug Release | Packaging – Form/Fill/Seal –  Heat Seal | **6** | **2** | **12**  **Undesirable** | **Severity:** Damaged, worn, or misaligned heat seal platens can result in poor heat seals. In addition, Incorrect heat seal temperatures can result in poor heat seals. Poor heat seals can result in compromised container closure integrity which directly impacts the stability, purity and efficacy of the finished drug product. It could potentially lead to an excessive of Oxybutynin Chloride, USP. The drug substance is Toxicologically safe and topically applied, OHC 3 and OEL 10 µg/m3, it will not adversely impact patient safety.  In addition, 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.  **Occurrence:** Within the evaluation period there are no instances of an OOS results for finished drug product. |

# Conclusions

The risk evaluation of hazards influenced by CMAs and critical process steps are provided in **Table 7**. These evaluations have identified undesirable risk levels to product CQAs based on influences by CMAs and critical process variables (see **Table 4** and **Table 5**). All other evaluations resulted in acceptable risk levels. The CMA/CQA and critical process steps/CQA relationships with undesirable risk levels listed in **Table 8** are quantitatively analyzed in the Potential Hazard Analysis (PHA) (see PRACS **Attachment 4**).

| Table 8: Factor / CQA Relationships with Undesirable or Unacceptable Risk Levels | | | |
| --- | --- | --- | --- |
| **Affected CQA** | **Ref. #** | **Influencing CMA/Critical Process Variable** | **Risk Category** |
| Assay | 1.1 | Oxybutynin Chloride, USP – Assay | **12 = Undesirable** |
| 1.7 | Packaging – Form/Fill/Seal – Machine Speed | **18 = Undesirable** |
| 1.8 | Packaging – Form/Fill/Seal – Heat Seal | **18 = Undesirable** |
| Minimum Fill | 2.1 | Packaging – Form/Fill/Seal – Machine Speed | **20 = Undesirable** |
| 2.2 | Packaging – Form/Fill/Seal – Heat Seal | **12 = Undesirable** |
| 2.3 | Packaging – Form/Fill/Seal – Fill Weight | **12 = Undesirable** |
| Ethanol | 4.1 | Dissolution of the drug substance and excipients in the main phase (Intermediate) – Disperser Mixer Speed | **12 = Undesirable** |
| 4.2 | Dissolution of the drug substance and excipients in the main phase (Intermediate) – Mixing Time | **12 = Undesirable** |
| 4.3 | Final Mixing (Intermediate) – Anchor Mixer Speed | **12 = Undesirable** |
| 4.4 | Final Mixing (Intermediate) – Mixing Time | **12 = Undesirable** |
| 4.5 | Final Mixing (Intermediate) – Disperser Mixer Speed | **12 = Undesirable** |
| 4.6 | Packaging – Form/Fill/Seal – Machine Speed | **18 = Undesirable** |
| 4.7 | Packaging – Form/Fill/Seal – Heat Seal | **18 = Undesirable** |
| Drug Release | 5.1 | Oxybutynin Chloride, USP – Assay | **12 = Undesirable** |
| 5.2 | Sachet Material – AQL | **20 = Undesirable** |
| 5.3 | Packaging – Form/Fill/Seal – Machine Speed | **20 = Undesirable** |
| 5.4 | Packaging – Form/Fill/Seal – Heat Seal | **12 = Undesirable** |

# References

| **Document Type** | **Document Name** | **Document #** |
| --- | --- | --- |
| Technical Report | Oxybutynin Chloride Topical Gel Formulation Development / Technology Transfer Report | TR-8709-27 |
| Validation Documents | Range Finding / Manufacturing Capability Study for Oxybutynin Gel, 100 mg/g, Processed using the 100-Gallon Mixer (Eq. # 01766) | M-0014-07 |
| Process Validation of Oxybutynin Chloride Gel 100 mg/g, (item 400132), Manufactured using 100-Gallon Mixer Eq. # 01766 | M-0030-07 |
| 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 |
| Oxybutynin Chloride, USP | 175037 |
| Purified Water, USP/EP | Plant System |
| Sodium Hydroxide, NF/EP | 175025 |
| Alcohol Ethanol, USP (96 Per Cent) | 175039 |
| Glycerin, USP / Glycerol, EP | 175024 |
| Hydroxypropyl Cellulose, NF | 175038 |
| Sachet Material | 208371 (US)  233173 (Canada) |