# Process Validation of Antidiabetic Drug Semaglutide

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***Abstract*****:** *The aim of research was to study process validation and risk evaluation and management of semaglutide tablet. Three batches of same size, method, equipment and validation criteria were taken. The critical process parameters involved in sifting, blending, lubrication, compression, coating, packaging and finished stage were identified and evaluated as per validation master plan. The validation showed that all in-process parameters and process variables were within acceptable limits. The results for process validation were as follows: Thickness (4.3±0.2), Hardness (NLT 4 kg/cm$^2$), Disintegration Time (NMT 30 min.), Dissolution (NLT 85% of label claim), Average weight (237.5 mg to 262.5 mg) and Assay (between 95 to 105 %). This process validation provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications*.

***Key words: Process Validation, Critical Process Parameters, Risk Management, Semaglutide.***

## 1. Introduction:

**Validation**

Validation is "Establishing documented evidence, which provides a high degree of assurance that specific process will consistently produce a product meeting its predetermined specification and quality attributes". [1]

USFDA defined process validation as "establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its pre determined specifications and quality characteristics".

Process validation is one of the important step in achieving and maintaining the quality of final product. It is the key element to assure the identity, purity, safety, efficacy and also maintaining the quality of final product. [2] It has three stages:

- Stage 1 – Process design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – Continued process verification: Ongoing assurance is gained during routine production that the process remains in a state of control.[3,4]

Process validation is divided in four types

- Prospective validation
- Retrospective validation
- Concurrent validation
- Revalidation[5]

**Risk management**

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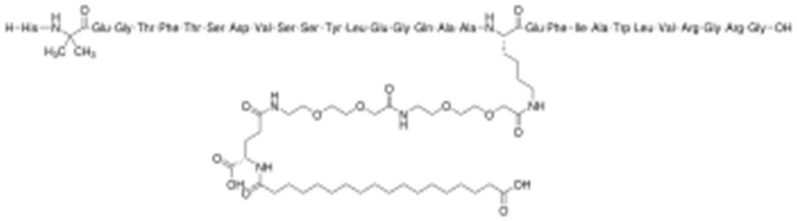
Risk management is the macro-level technique of assessing, analyzing, prioritizing, and making a strategy for mitigating threats and managing risk to an organization's assets and earnings. ICH Q9 defined risk management as "The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk"[6] The seriousness of a risk can be determined by multiplying the probability of the event actually occurring by the potential negative impact to the cost, schedule, or performance of the project.

## 2. Drug Profile[7-10]

Drug Name: Semaglutide
Molecular Formula- C187H291N45O59
Molecular Weight- 4113.641
Structure:



Pharmacokinetic Parameters:

- Bioavailability in the tablet form- >89%
- Protein binding- 94-98%
- Metabolism- Hepatic
- Elimination Half life- 7days
- Excretion- 50% renal, 46% biliary

Pharmacological Actions:
A polypeptide that contains a linear sequence of 31 amino acids joined together by peptide linkages. It is an agonist of glucagon-like peptide-1 receptors (GLP-1 AR) and used for the treatment of type 2 diabetes. Semaglutide is an anti-diabetic medication used for the treatment of type 2 diabetes and an anti-obesity medication used for long-term weight management. It is a peptide similar to the hormone glucagon-like peptide-1 (GLP-1), modified with a side chain. It can be administered by subcutaneous injection or taken orally.
Adverse Effects:
Serious adverse drug reaction associated with Semaglutide therapy includes:

- Nausea,
- Vomiting
- Diarrhea
- Abdominal pain
- Constipation.

Dosage of Semaglutide tablet: 7 mg

## 3. Materials and Method:

### 3.1 Materials:

The Excipients used in tablet manufacturing are: Semaglutide, Betadex, Micro crystalline cellulose, Ac-Di-Sol (Croscarmellose sodium), Maize starch, Purified talc, Magnesium stearate, Hydroxy propyl

methyl cellulose, Isopropyl alcohol, Methylene chloride, Titanium dioxide, Propylene glycols and Red oxide of iron.

The Equipments and Instruments used are: Digital Vernier Callipers, Friability test apparatus, Blister machine, Leak test apparatus, HPLC, Dissolution apparatus, UV-Spectrophotometer, Analytical weighing balance, Mechanical vibrator sifter with 16#,20#,40#,60#,100# sieve (wire wove), Contra blender, 35th station double rotary machine with 9 mm oval shaped punches, plain on upper& lower punches, Neocota (auto coater), SS vessels with lid 150 ft, Monsanto hardness tester and Disintegration test apparatus.

### 3.2 Product details:

**Table 1: Product Details**

| | |
|---|---|
| **Product** | Semaglutide Tablet |
| **Batch Size** | 5,00,000 Tablets |
| **Dosage Form** | Solid dosage form(tablets) |
| **Shelf Life** | 24 Months |
| **Type of Validation** | Concurrent |
| **Label Claim:**<br>Each film coated tablet contains<br>Semaglutide ---------- 7 mg<br>Excipients ---------- q.s.<br>Colors: Red oxide of Iron and Titanium Dioxide BP | |

### 3.3 Method:

Three batches of 5,00,000 Tablets batch size were manufactured and observations were recorded at various stages. Yield after completion of Compression, Coating and Packing process were recorded.

**Sifting:** Sifting stage is carried out for distribution of particle size of the all ingredients, different sieves of different mesh size were used for uniform distribution of all ingredients. Mechanical sifter is used for this purpose. Sift Semaglutide & Betadex BP through 40 # sieve by using sifter. Sift Microcrystalline cellulose (Sancel pH 102) BP through 20 # sieve by using sifter. Sift Ac-Di-Sol (Croscarmellose sodium) BP through 30 # sieve by using sifter. Sift Maize Starch BP through 60 # sieve by using sifter. Sift Purified Talc BP & Magnesium stearate BP through 60 # sieve.

**Blending:** The blending step involves blending of all sifted active ingredients using contra blender. The purpose is to get a uniform distribution of ingredients. This is followed by mixing magnesium stearate in Contra blender to get good flow and anti-adhesion property of the blend. The bulk of uniformity of active has to establish during validation of blending process. The criteria for the bulk of uniformity of Semaglutide was considered and should be within 95% to 105 % of the Label claim, the blending of the active ingredient depends on the blending time, which affects the uniform distribution of drug. Hence it is a critical step to be validated. Blending time is critical as under blending will result in non-uniform distribution of drug and poor flow whereas over blending will result in de-mixing leading to non-uniform distribution of drug and increase in disintegration time. Blending was carried out for 30 minutes at 8 RPM. Testing Parameters such as Bulk of Uniformity, RSD (%), Carr's index (%), Hausner's ratio and Flow property are monitored.

**Lubrication:** Lubrication step is followed by blending process, in lubrication stage the mixed ingredients are lubricated with magnesium stearate and talc in contra blender at 8 RPM for 5 minutes.

This lubrication stage is carried out for proper compression of the blended material. Testing Parameters such as Blend Uniformity, RSD (%), Carr's index (%), Hausner's ratio and Flow property are monitored.

**Compression:** This step involves conversion of blended material into tablets as per specifications. Compression process involves an elaborate validation program as the change in physical parameters of the tablets tends to affect the other critical parameters. The tablets compressed at three different speeds were checked for all the physical parameters as per the specifications. The in-process physical parameters are checked as per the frequency mentioned in the respective Batch Manufacturing Record. Speed of the machine is major variable. Compress the granules using stationary double rotary machines with 9.0 mm oval shaped punch, plain on both sides.

**Table 2: Testing parameters and limits**

| **Parameters** | **Limits** |
|---|---|
| Description | A white colored uncoated tablet; plain from both sides. |
| Average weight | 250 mg $\pm$ 5 % (Min 237.5 mg, Max 262.5 mg) |
| Uniformity of weight | 250 mg $\pm$ 5 % (Min 237.5 mg, Max 262.5 mg) |
| Thickness | 4.2 $\pm$ 0.2 mm (Min 4.0 mm, Max 4.4 mm) |
| Hardness | Not less than 4.0 Kg /$cm^2$. |
| Friability | Not more than 1.0 %. |
| Disintegration time | Not more than15 Minutes |
| Assay | 95 % to 105 % of Label claim |
| Dissolution | Not less than 85 % of Label claim |
| Uniformity of dosage unit | 85 % to 115 % of Label claim and Relative standard deviation less than or equal to 6 % |

**Coating:** The Coating step involves the covering of tablet surface with a polymer film. In coating process pan RPM, inlet temperature, exhaust temperature, spray rate and atomization air pressure are critical process variables. These parameters affect the coating and final appearance of the tablets.

**Table 3: Fixed parameters and limits in coating process**

| **Parameters** | **Limits** |
|---|---|
| Pan Speed | 5-7 RPM |
| Inlet temp. | 50 °C-60 °C |
| Exhaust air temp. | 40 °C to 45 °C |
| Tablet Bed temp. | 45 °C-55 °C |
| Spray rate | 200-300 ml/min |
| Atomization air pressure | 2.0 - 2.5 Kg/$cm^2$ |

**Table 4: Testing parameters and limits in coating process**

| **Parameters** | **Limits** |
|---|---|
| Description | An oval shaped film coated tablet, plain on both sides |
| Uniformity of weight | 250 mg ± 5.0 % (Min 237.5 mg, Max 262.5 mg) |
| Average weight | 250 mg ± 5.0 % (Min 237.5 mg, Max 262.5 mg) |
| Thickness | 4.3 ± 0.2 mm (4.1 mm to 4.5 mm) |

| | |
|---|---|
| Disintegration time | Not more than 30 minutes |
| Dissolution | Not less than 85 % of label claim |
| Assay | 95 % to 105 % of label claim |
| Hardness | Not less than 4.0 kg/cm$^2$ |

**Packing:** This process involves packing of tablets in polythene lined aluminium foils and blister bottom cold form aluminium foil blister pack. Sealing roller temperature & speed of machine are critical variables. Adequate sealing roller temperature is essential to get proper sealing. Less temperature will lead to leakage and higher temperature will result in burning or spoilage of aluminum foil. Packing was carried out at speed 60-80 cuts per minutes, sealing temperature 170-180˚C and forming temperature 140-150˚C. Testing Parameters such as Leak test and Printing quality are carried out. Speed of the machine is influenced by following parameters.

- Proper sealing of blister pack
- Proper forming of blister pack

**Finished Product:**

**Table 5: Finished Product Specifications**

| Sr.No. | Parameters | Limits |
|---|---|---|
| 1. | Description | An oval shaped film coated tablet, plain on both sides. |
| 2. | Uniformity of Weight | 250 mg $\pm$ 5 % (Min 237.5 mg, Max 262.5 mg) |
| 3. | Average weight | 250 mg $\pm$ 5 % (Min 237.5 mg, Max 262.5 mg) |
| 4. | Hardness | Not less than 4 kg/cm$^2$ |
| 5. | Thickness | 4.3 ± 0.2 mm (Min 4.1 mm, Max 4.5 mm) |
| 6. | Disintegration Time | Not more than 30 minutes |
| 7. | Dissolution | Not less than 85 % of label claim in 30 minutes |
| 8. | Uniformity of dosage unit | Between 85 % to 115 % & relative standard deviation less than or equal to 6.0 % |
| 9. | Assay of Semaglutide eq. to Semaglutide | Between 95 % to 105 % on Label Claim 7 mg |
| 10. | Related compounds | Not more than1.2 % of Semaglutide related compound A<br>Not more than 1.5 % of Semaglutide related compound C<br>Not more than 0.2 % of any single impurity excluding of Semaglutide related compound B<br>Not more than 2.5 % of total impurities excluding Semaglutide related compound B |
| 11. | Microbiological purity<br>Total viable count<br>Total fungal count<br>Pathogen | <br>Not more than $10^3$ cfu/gm<br>Not more than $10^2$ cfu/gm<br>Must be absent |

**Yield Details:** Yield was recorded at stages mentioned below:

- Mixing
- Compression
- Coated tablet
- Packing

**Risk Management and Evaluation:** At the time of manufacturing of Semaglutide tablet, risks were found at different stages like sifting, blending, lubrication, compression, coating, packing due to different causes. These risks were managed by risk management process which includes risk identification, risk analysis and evaluation. Evaluation of risk was done by risk priority number (RPN) which is multiplication of probability, severity and detection of the risk. Risk priority number is divided into three sets. Minor (1-9), Major (10-18), Critical (19-27).

## 4. Result and Discussion:

**SIFTING:** Sieve integrity was found ok before and after sifting raw material and % retention was nil for all three batches.

**BLENDING:**

**Table 6: Results of blend uniformity and flow properties after blending**

| Batch | Blend uniformity (%) | % RSD | Untapped density ($gm/cm^3$) | Tapped density ($gm/cm^3$) | Carr's index (%) | Hausner's ratio | Flow property |
|---|---|---|---|---|---|---|---|
| 1 | 99.47 | 0.239 | 0.45 | 0.50 | 10.00 | 1.11 | OK |
| 2 | 99.49 | 0.412 | 0.48 | 0.56 | 14.28 | 1.16 | OK |
| 3 | 99.55 | 0.312 | 0.48 | 0.56 | 14.28 | 1.16 | OK |

**LUBRICATION:**

**Table 7: Results of blend uniformity and flow properties after lubrication**

| Batch | Blend uniformity (%) | % RSD | Untapped density ($gm/cm^3$) | Tapped density ($gm/cm^3$) | Carr's index (%) | Hausner's ratio | Flow property |
|---|---|---|---|---|---|---|---|
| 1 | 99.69 | 0.425 | 0.46 | 0.49 | 6.12 | 1.06 | OK |
| 2 | 99.71 | 0.451 | 0.46 | 0.51 | 9.80 | 1.10 | OK |
| 3 | 99.76 | 0.459 | 0.49 | 0.55 | 10.90 | 1.12 | OK |

**COMPRESSION:**

**Table 8: Results of variables monitored during compression**

| Parameters | Speed | Batch 1 | | Batch 2 | | Batch 3 | |
|---|---|---|---|---|---|---|---|
| | | Station 1 | Station 2 | Station 1 | Station 2 | Station 1 | Station 2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dissolution (%) | Slow | 97.65 | 98.05 | 95.0 | 96.0 | 99.35 | 99.0 |
| | Medium | 98.05 | 98.20 | 97.20 | 98.30 | 99.30 | 99.35 |
| | High | 98.02 | 98.65 | 97.68 | 97.45 | 98.01 | 98.10 |
| Assay (%) | Slow | 101.32 | 101.29 | 102.35 | 102.50 | 103.35 | 103.20 |
| | Medium | 100.00 | 99.38 | 99.36 | 102.30 | 10130 | 102.36 |
| | High | 101.32 | 100.33 | 100.32 | 100.33 | 101.33 | 102.0 |
| Uniformity of Dosage unit (%) | Slow | 98.51 | 98.99 | 99.38 | 99.00 | 99.03 | 99.38 |
| | Medium | 98.62 | 98.96 | 98.40 | 98.63 | 98.90 | 98.66 |
| | High | 99.12 | 99.44 | 98.78 | 98.84 | 98.89 | 98.75 |
| Friability (%) | Slow | 0.25 | 0.24 | 0.28 | 0.30 | 0.33 | 0.38 |
| | Medium | 0.28 | 0.32 | 0.40 | 0.41 | 0.41 | 0.29 |
| | High | 0.30 | 0.32 | 0.38 | 0.36 | 0.38 | 0.35 |
| Disintegration Time (min.) | Slow | 8 min.32 sec. | 8 min. 37 sec. | 8 min. 5 sec. | 7 min. 55 sec. | 8 min. | 8 min. 10 sec. |
| | Medium | 7 min. 54 sec. | 7 min. 40 sec. | 7 min. 47 sec. | 7 min. 35sec. | 7 min. 16 sec. | 7 min. 47 sec. |
| | High | 7 min. 11 sec. | 7 min. 26 sec. | 7 min. | 7 min.14 sec. | 7 min. 10 sec. | 7 min. 30 sec. |
| Average Weight (mg) | Slow | 250.28 | 250.48 | 250.28 | 250.22 | 250.43 | 250.26 |
| | Medium | 250.05 | 250.08 | 249.90 | 249.92 | 250.02 | 249.91 |
| | High | 249.94 | 249.98 | 249.88 | 249.94 | 249.93 | 249.90 |
| Uniformity of Weight (mg) | Slow | 250.60 | 250.62 | 251.10 | 251.63 | 251.14 | 251.61 |
| | Medium | 250.15 | 250.00 | 250.05 | 250.54 | 250.54 | 249.90 |
| | High | 249.51 | 249.86 | 249.61 | 249.12 | 249.62 | 249.84 |
| Hardness ($kg/cm^2$) | Slow | 4.00 | 414 | 4.20 | 4.54 | 4.35 | 4.45 |
| | Medium | 4.02 | 4.03 | 4.02 | 4.14 | 3.99 | 3.98 |
| | High | 3.98 | 4.00 | 3.80 | 3.75 | 3.87 | 3.75 |
| Thickness (mm) | Slow | 4.29 | 4.44 | 4.28 | 4.31 | 4.30 | 4.33 |
| | Medium | 4.30 | 4.30 | 4.27 | 4.26 | 4.22 | 4.28 |
| | High | 4.28 | 4.24 | 4.20 | 4.22 | 4.21 | 4.20 |

**COATING:**

**Table 9: Results of variables monitored during coating**

| **Parameter** | **Lot** | **Batch 1** | **Batch 2** | **Batch 3** |
|---|---|---|---|---|
| Assay (%) | 1 | 100.72 | 100.25 | 100.77 |
| | 2 | 101.78 | 100.22 | 100.72 |
| Dissolution (%) | 1 | 98.69 | 99.69 | 98.69 |
| | 2 | 97.95 | 99.10 | 98.47 |
| Disintegration time (min.) | 1 | 8 min. 40 sec. | 7 min. 58 sec. | 8 min. 5 sec. |
| | 2 | 8 min. 30 sec. | 7 min. 36 sec. | 8 min. 14 sec. |
| Uniformity of weight (mg) | 1 | 257.35 | 255.15 | 256.65 |
| | 2 | 258.54 | 256.40 | 257.55 |
| Average weight (mg) | 1 | 257.56 | 255.25 | 256.12 |

| | | | | |
|---|---|---|---|---|
| | 2 | 257.20 | 256.45 | 256.98 |
| Hardness (kg/cm$^2$) | 1 | 4.15 | 4.04 | 4.25 |
| | 2 | 4.25 | 4.25 | 4.20 |
| Thickness (mm) | 1 | 4.38 | 4.24 | 4.44 |
| | 2 | 4.40 | 4.41 | 4.30 |

**Table 10: Observed coating parameter**

| Process Parameter | Range | | |
|---|---|---|---|
| | **Batch 1** | **Batch 2** | **Batch 3** |
| Pan RPM | 5 - 7 RPM | 5 - 7 RPM | 5 to 7 RPM |
| Inlet air temperature | 50 ºC to 60 ºC | 50 ºC to 60 ºC | 50 ºC to 60 ºC |
| Exhaust air temperature | 40 ºC to 45 ºC | 40 ºC to 45 ºC | 40 ºC to 45 ºC |
| Spray rate | 200 - 300 ml/min | 200 - 300 ml/min | 200 - 300 ml/min |
| Atomization air pressure | 2.0 to 2.5 kg/cm$^2$ | 2.0 to 2.5 kg/cm$^2$ | 2.0 to 2.5 kg/cm$^2$ |
| Bed temperature | 45 ºC to 55 ºC | 45 ºC to 55 ºC | 45 ºC to 55 ºC |

**PACKING:**

**Table 11: Results of variables monitored during packing**

| **Parameters** | **Batch 1** | **Batch 2** | **Batch 3** |
|---|---|---|---|
| Speed | 60-80 cuts/min. | 60-80 cuts/min. | 60-80 cuts/min. |
| Sealing temperature | 170-180˚C | 170-180˚C | 170-180˚C |
| Forming temperature | 140-150˚C | 140-150˚C | 140-150˚C |
| Printing quality | OK | OK | OK |
| Leak test | No Leak were found | No Leak were found | No Leak were found |

**FINISHED PRODUCT:**

**Table 12: Results of critical quality attributes of finished product**

| **Parameter** | **Stage** | **Batch 1** | **Batch 2** | **Batch 3** |
|---|---|---|---|---|
| Assay (%) | Initial | 100.96 | 101.21 | 100.63 |
| | Middle | 101.35 | 100.87 | 100.31 |
| | End | 101.54 | 100.74 | 100.72 |
| Dissolution (%) | Initial | 98.69 | 99.09 | 97.95 |
| | Middle | 98.35 | 99.36 | 98.05 |
| | End | 98.79 | 98.95 | 98.24 |
| Uniformity of dosage unit (%) | Initial | 99.37 | 98.59 | 98.45 |
| | Middle | 99.50 | 99.32 | 99.54 |
| | End | 98.90 | 99.19 | 99.13 |
| Uniformity of weight (mg) | Initial | 257.35 | 255.15 | 256.65 |
| | Middle | 257.85 | 255.98 | 257.20 |
| | End | 258.54 | 256.40 | 257.55 |
| | Initial | 257.56 | 255.25 | 256.12 |

| | | | | |
|---|---|---|---|---|
| Average weight (mg) | Middle | 257.78 | 255.65 | 256.54 |
| | End | 257.20 | 256.45 | 256.98 |
| Hardness ($kg/cm^2$) | Initial | 4.15 | 4.20 | 4.05 |
| | Middle | 4.23 | 4.12 | 4.14 |
| | End | 4.23 | 4.16 | 4.20 |
| Thickness (mm) | Initial | 4.28 | 4.32 | 4.40 |
| | Middle | 4.31 | 4.35 | 4.30 |
| | End | 4.32 | 4.28 | 4.25 |
| Disintegration time (minutes) | Initial | 7 min. 40 sec. | 7 min. 12 sec. | 8 min. 14 sec. |
| | Middle | 7 min. 11 sec. | 7 min. 5 sec. | 8 min. 2 sec. |
| | End | 7 min. 33 sec. | 7 min. 22 sec. | 8 min. 29 sec. |
| Total viable count (cfu/gm) | Initial | 50 | 60 | 54 |
| | Middle | 68 | 58 | 64 |
| | End | 54 | 70 | 50 |
| Total fungal count | Initial | Nil | Nil | Nil |
| | Middle | Nil | Nil | Nil |
| | End | Nil | Nil | Nil |
| Pathogens | Initial | Absent | Absent | Absent |
| | Middle | Absent | Absent | Absent |
| | End | Absent | Absent | Absent |
| Related compounds | Initial | Pass | Pass | Pass |
| | Middle | Pass | Pass | Pass |
| | End | Pass | Pass | Pass |

**YIELD DETAILS:**

**Table 13: Yield Monitored at Processing Stages**

| **Processing Stage** | **Yield (%)** | **Batch 1** | **Batch 2** | **Batch 3** |
|---|---|---|---|---|
| Blending | Theoretical yield | 125.00 | 125.00 | 125.00 |
| | Actual yield | 124.38 | 124.35 | 124.12 |
| | Percentage yield | 99.50 | 99.48 | 99.29 |
| Compression | Theoretical yield | 125.00 | 125.00 | 125.00 |
| | Actual yield | 124.04 | 124.15 | 124.56 |
| | Percentage yield | 99.23 | 99.32 | 99.64 |
| Coating | Theoretical yield | 127.50 | 127.50 | 127.50 |
| | Actual yield | 126.48 | 126.12 | 126.98 |
| | Percentage yield | 99.20 | 98.91 | 99.59 |
| Packing | Theoretical yield | 5,00,000 | 5,00,000 | 5,00,000 |
| | Actual yield | 4,89,600 | 4,92,600 | 4,88,800 |
| | Percentage yield | 97.92 | 98.52 | 97.76 |

**RISK IDENTIFICATION AND EVALUATION:**

**Table 14: Risk Identification and Evaluation**

P= Probability, S= Severity, D= Detection, RPN= Risk Priority Number

| Sr. No. | Activity | Possible Risk/Failure (Identified Risk) | Potential Causes Of The Identified Risk And Consequences | Risk Analysis and Evaluation | | | | Current Control Measures |
|---|---|---|---|---|---|---|---|---|
| | | | | P<br>1 | S<br>2 | D<br>3 | RPN<br>(1*2*3) | |
| 1 | Vendor development | Material from non-approved vendor | Receipt of non-compliant material to the quality requirement | 2 | 2 | 1 | 4 | Vendor approval system is in place. Evaluation of vendor is carried out before the material is supplied. Indent / Order are given only to approve vendor. Approved Vendor list is made available at the warehouse receipt stage. |
| 2 | Receipt of Raw Material | Mix up of material during receipt. | Mix-up of Raw Material at Vendor end. (If Vendor manufactures different raw materials). | 1 | 3 | 1 | 3 | Received material is checked against order before starting receipt activity. Each batch of the consignment is segregated material is stored separately on pallet batch wise. Each container is labeled with identification label (Quarantine Label). |
| | | | Different batches of same material received in a consignment | 3 | 2 | 1 | 6 | Different batch of the material is adequately separated from each other and identified with different GRA number. |
| 3 | Storage of Material in Quarantine | Mix up of material | No Batch wise segregation during storage. | 1 | 3 | 1 | 3 | Different batch of the material is adequately separated from each other. |
| 4 | Sampling of Raw Material | Mix-up / Cross Contamination | Wrong labeling during receipt – Quarantine label | 2 | 3 | 1 | 6 | Sampling chemist verifies GRA raised by warehouse, vendor label on each container and Quarantine label to confirm materials. |
| | | | Sampling is not done at a time for one batch. | 1 | 3 | 2 | 6 | For Inspection & sampling procedure Raw materials provides instruction for sampling of only one batch at a time in the sampling booth. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Cleaning procedure not followed. | 1 | 3 | 2 | 6 | Operation & Cleaning of sampling booth and area and Cleaning sampling accessories provides instructions for cleaning of sampling devices and area followed by proper status labeling. |
| | | | Cleanliness of area | 1 | 3 | 2 | 6 | The area is qualified for class 1, 00,000 requirements and provided with reverse laminar air flow unit. AHU system performance verification is carried out every year. Routine environmental monitoring is carried out. |
| 5 | Transfer and storage of approved Raw material to Approved Area. | Mix-up of material | Material stored near Un tested material. Material segregation not done. | 1 | 2 | 1 | 2 | Proper Identification of Approved and quarantine areas shown with area demarcation and materials status is also indicated with status labeling. |
| 6 | Dispensing of Raw material. | Cross Contamination | Improper segregation of 'under test', and 'Approved' materials in warehouse area. | 2 | 3 | 1 | 6 | provide instructions for dispensing of Raw materials after checking Approved Status by Stores, before start dispensing QA verified the same as per of Batch manufacturing record. |
| 7 | Receipt of Packing material | Mix-up of the consignment | Supply of the material for different firms by the same vendor in the same vehicle | 2 | 3 | 1 | 6 | Instructions for inspection are During receiving checked the materials as per checklist. |
| | | | Different batches of same material received in a consignment | 1 | 3 | 2 | 6 | Different batch of the material is adequately separated from each other and identified with different GRA number. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Label torn out. | 2 | 3 | 1 | 6 | Vendor approval procedures to ensure to follow proper labeling and identification procedures during dispatch. During receipt each container / pack is observed for damage container as per the instruction provided |
| 8 | Storage | Mix-up of the consignment | No Batch wise segregation during storage. | 1 | 3 | 2 | 6 | Different batch of the material is adequately separated from each other and identified with different GRA number as instructions provided. |
| | | | During storage, if loose boxes are not sealed properly. | 2 | 2 | 2 | 8 | Inspection and Sampling of Packaging Materials, packages are sealed immediately after sampling. |
| | | Incorrect status label while storage | No trained personnel | 2 | 2 | 1 | 4 | Training of Personnel ensures no untrained personnel are allowed to perform any activity. Before dispensing Activity checked the Materials By Stores /IPQA |
| 9 | Sampling of Packing material | Mix-up of Packing Material | Untrained personnel for sampling | 2 | 2 | 1 | 4 | Training of Personnel ensures no untrained personnel are allowed to perform sampling activity. |
| 10 | Dispensing of Packing material | Mix-up of material | No procedure for dispensing of packing material | 2 | 3 | 1 | 6 | Provides instruction for issuance packing material. During dispensing of packing materials Stores take the line clearance from IPQA that will reflect in batch packing record |
| | | | Line clearance not done | 2 | 3 | 1 | 6 | Provides instructions for carrying out dispensing activity after line clearance from QA personnel as per respective batch packing record. |
| 11 | Staging (Dispensed material) | Mix-up | Wrong identification labels/torn | 2 | 2 | 2 | 8 | The labels are written during dispensing by warehouse person and counter signed by |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | labels/labels are not legible. | | | | | Packing officer who witnesses dispensing activity. All individual Packing materials are kept in box /crate is labeled with "Dispensed Packing material" label. |
| 12 | Granulation | Mix-up / Cross contamination | Line clearance not taken. | 1 | 3 | 2 | 6 | As per BMR, Verification of area, labeling status, logs and conditions are checked during the Line Clearance Procedure and activities are commenced after QA Approval and recorded in the BMR. |
| | | | Type A and B cleaning not followed. | 1 | 3 | 1 | 3 | During verification of dispensed materials by IPQA noticed either clearance taken or not, materials verification reflect on BMR |
| 13 | Compression | Mix-up / Cross contamination | Line clearance not taken. | 2 | 3 | 2 | 12 | As per BMR, Verification of area, labeling status, logs and environmental conditions are checked during the Line Clearance Procedure and activities are commenced after IPQA Approval and recorded in the BMR. |
| 14 | Coating | Mix-up | Line clearance not taken. | 2 | 3 | 2 | 12 | As per BMR, Verification of area, labeling status, logs and environmental conditions are checked during the Line Clearance Procedure and activities are commenced after IPQA Approval and recorded in the BMR. |

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|---|---|---|---|---|---|---|---|---|
| | | | Type A and B cleaning not followed. | 1 | 3 | 1 | 3 | As per BMR, Verification of cleaning activity is done during the Line Clearance and activities are commenced after IPQA Approval and recorded in the BMR.<br>For A type cleaning (Product to Product) IPQA checked the Rinse / Swab report<br>For B type cleaning (Batch to Batch) IPQA checked Visual clean |
| 15 | Blistering /Striping operation. | Mix-up | Line clearance not taken. | 2 | 3 | 2 | 12 | As per BPR, Verification of area, labeling status, logs and environmental conditions are checked during the Line Clearance Procedure and activities are commenced after IPQA Approval and recorded in the BPR. |
| 16 | Packing | Mix-up | General arrangement and Layout of packing hall not proper. | 2 | 3 | 2 | 12 | As per the layout each packing line is independent and well segregated from other lines so as to avoid any mix-ups. |
| | | | Incorrect carton used. | 2 | 3 | 2 | 12 | While dispensing checking of item codes against the BPR carried out by stores and Packing personnel.<br>Verification of dispensed packing material by IPQA during line clearance.<br>Carton identification carried out by art works code.<br>In-process checks by packing officer and IPQA at defined intervals. |
| 17 | Storage of Finished Product | Mix-up | Finished product not labeled. | 2 | 3 | 1 | 6 | Online shipper labeling is done with product details and same is recorded in BPR.<br>Storage and Handling of Finished Goods, the warehouse officer shall examine the cases for proper labeling prior to accepting the packed goods. |

## 5. Conclusion:

The Concurrent process validation of Semaglutide Tablet was studied. It gives detail about the validation of each step of the manufacturing process. Based on result and conclusion, it is established that the employed manufacturing process is capable to produce the product consistently which meets all the predetermined specification and quality attributes. Hence the manufacturing process stands validated and can be used for routine manufacturing of Semaglutide tablet. At the time of manufacturing of Semaglutide tablet, risks were found at different stages of manufacturing due to different causes. Evaluation of risk was done by risk priority number (RPN) which is multiplication of probability, severity and detection of the risk.

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