PROCESS VALIDATION OF FLUCONAZOLE

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ABSTRACT

Validation is the act of demonstrating and documenting that a procedure operates effectively. The U.S Food and Drug Administration (FDA) guidelines state that the process validation is the established documented evidence which provides a high degree of assurance that specific process. Fluconazole is a triazole antifungal drug used in the treatment and prevention of superficial and systemic fungal infections. In a bulk Powder form, it appears as a white crystalline powder, and it is very slightly soluble in water and soluble in alcohol. It is designated as 2,4-difluoro-bis(1H-1,2,4-triazol-1-ylmethyl) benzyl alcohol with an empirical formula of C_{13}H_{12}F_{2}N_{6}O and molecular weight 306.3.
KEYWORDS

Onychomycosis, Candida, Tinea corporis, Antifungal.

INTRODUCTION

CHEMICAL DATA:
Formula           :   C₁₃H₁₂F₂N₆O
Molecular Mass    :   306.27 g/mol

PHARMACOKINETIC DATA:
Bioavailability   :   >90%
Protein binding   :   11 to 12%

Assurance of product quality is derived from careful and systemic attention to a number of important factors like selection of quality parts and materials, adequate product and process design, process control and final product testing. Current Good Manufacturing Practices (CGMP) regulations demands written procedures for production and process controls to assure that the drag (Please check spelling is it ‘drug’?) products have the identity, strength, quality, and purity.

U.S. FDA’s CGMP guidelines state that control procedures should be established to monitor the product and to validate the performance of the manufacturing processes. Control procedures like weight variation, disintegration time, mixing time to assure uniformity and homogeneity, dissolution time and dissolution rate are related to the manufacturing and validation of solid dosage forms. Clarity, completeness and pH tests are related to the manufacturing and validation of liquid dosage forms. Process Validation is to be done for the critical manufacturing steps laid down in the approved Master Formula as bulk stage and finished product stage. In the manufacturing processes, a minimum of three production runs or three repetitive steps to be selected.

Like other imidazole- and triazole-class antifungal, fluconazole inhibits the fungal cytochrome P450 enzyme 14α-demethylase. Mammalian demethylase activity is much less sensitive to fluconazole than fungal demethylase. This inhibition prevents the conversion of lanosterol to ergosterol, an essential component of the fungal cytoplasm membrane, and subsequent accumulation of 14α-methyl sterols. Fluconazole is primarily fungistatic however may be fungicidal against certain organisms in a dose-dependent manner. Interestingly, when fluconazole was in development at Pfizer, it was decided early in the process to avoid producing any chiral centers in the drug so that subsequent synthesis and purification did not encounter difficulties with enantiomer separation and associated variations in biological effect. A number of related compounds where found to be extremely potent teratogens and subsequently discarded.

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Bioequivalence was established between the 100 mg tablet and both suspension strengths when administered as a single 200 mg dose.

Peak plasma concentrations (Cmax) in fasted normal volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of approximately 30 hours (range: 20-50 hours) after oral administration.

In fasted normal volunteers, administration of a single oral 400 mg dose of DIFLUCAN (fluconazole) leads to a mean Cmax
of 6.72 μg/mL (range: 4.12 to 8.08 μg/mL) and after single oral doses of 50-400 mg.

**MATERIALS AND METHODS**

**FOR FLUCONAZOLE-III**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>INGREDIENTS</th>
<th>STD. QTY</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL –II</td>
<td>Caustic potash flakes (CP Flakes)</td>
<td>150kg</td>
</tr>
<tr>
<td></td>
<td>Tri methyl sulfoxonium iodide (TMSI)</td>
<td>215kg</td>
</tr>
<tr>
<td>FL - III</td>
<td>1-H-1,2,4 Triazole</td>
<td>105kgs</td>
</tr>
<tr>
<td></td>
<td>Citric Acid</td>
<td>5 Kg.</td>
</tr>
<tr>
<td></td>
<td>Ethyl Acetate</td>
<td>60L</td>
</tr>
<tr>
<td></td>
<td>Acetone</td>
<td>40L</td>
</tr>
<tr>
<td></td>
<td>Toluene</td>
<td>750L</td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
<td>5 L</td>
</tr>
<tr>
<td></td>
<td>Hydrochloric acid (HCL)</td>
<td>95-100kg</td>
</tr>
<tr>
<td></td>
<td>D.M. Water</td>
<td>2200L</td>
</tr>
</tbody>
</table>

**FLUCONAZOLE-FINAL**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>INGREDIENTS</th>
<th>STD. QTY</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL –III</td>
<td>Citric Acid</td>
<td>13Kg.</td>
</tr>
<tr>
<td></td>
<td>Ethyl Acetate</td>
<td>100L</td>
</tr>
<tr>
<td></td>
<td>Acetone</td>
<td>200L</td>
</tr>
<tr>
<td></td>
<td>Toluene</td>
<td>10L</td>
</tr>
<tr>
<td></td>
<td>Hydrochloric Acid</td>
<td>150kg</td>
</tr>
<tr>
<td></td>
<td>Methyl dichloride</td>
<td>400L</td>
</tr>
<tr>
<td></td>
<td>Activated Carbon</td>
<td>8kg</td>
</tr>
<tr>
<td></td>
<td>Hyflowe</td>
<td>3kg</td>
</tr>
<tr>
<td></td>
<td>EDTA</td>
<td>4kg</td>
</tr>
<tr>
<td></td>
<td>Ammonia Solution</td>
<td>120kg</td>
</tr>
<tr>
<td></td>
<td>D.M. Water</td>
<td>1325L</td>
</tr>
</tbody>
</table>
FLUCONAZOLE-I

**METHODOLOGY**

- Charge 100Lts of MDC in GLR -206. Cool to 5-7°C
- Charge 125kgs of 1,3 – Diflugenzene in GLR -206 at 5-7°C
- Charge 160kgs of Aluminum Chloride in GLR-206 at 5-7°C
- Add slowly 140kgs of CAC over a period of 4-5 hrs at 5-45°C
- Rise the Mass temperature to 20-25°C
- Maintain the R.M. for 4hrs at 20-25°C
- Rise the R.M. temperature to 30-35°C by hot water circulation.
- Maintain the RM for 7 hrs at 30-35°C
- Send a sample of R.M. to Qc for G.C analysis.
- (Limit : -1,3- Difluro benzene NMTO. 5%)
- If reaction is not complete , Maintain for 60 min max and recheck the
- 1,3 – Difulro benzene content by G.C
- If Reaction is complete , cool the RM to 10-5°C
- Charge 12No’s of Ice blocks & 60kgs of Hcl In PPFR reactor (PPR-212).
- Transfer the RM slowly over period of 60-90min below 25°C from GLR-206 to PPR -212
- Rise (GLR – 206) with 100 Lts of MDC and transfer the wasting
- Stir for 30min and settle for 30min
- Separate the organic layer in the PPRC-212 A.
- Charge 200lts of MDC to aqueous layer in PPR-212A.
- Stir for 30min and stir for 30min
- Separate the organic layer in to PPRc -212A.
- Charge 200 Lts of MDC to aqueous layer in PPRC -212A.
- Stir for 30min and settle for 30min
- Separate the organic layer in to PPRC-212A.
- Charge 200lts of MDC to aq layer in PPR-212.
- Stir for 30 min and settle for 30min
- Separate the organic layer in to PPRC-212 a and drain the aqueous layer in ETP
- Charge the total organic Layer in PPR-212.
- Charge 300ltr D.M. water.
- Stir for 30min and settle for 30 min
- Separate the organic layer in SR -207/SSR-205.
- Charge 200lts MDC to aqueous layer in PPR – 212
- Stir for 30min and settle for 30min
- Separate the organic layer into SSR – 207/SSR-205.
- Distilled out MDC at 50-55°C (Use hot water circulation)
- Remove the MDC traces at 50-55°C under vacuum over a period of 2 hrs
- Cool R.M. temperature to 25-30°C

**COMPONENTS**

<table>
<thead>
<tr>
<th>Component</th>
<th>STD Qty</th>
<th>Actual Qty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3-Difulora Benzene (1,3-DFB)</td>
<td>125 kgs</td>
<td>125 kgs</td>
</tr>
<tr>
<td>Aluminum Chloride</td>
<td>160 kgs</td>
<td>160 kgs</td>
</tr>
<tr>
<td>4-Amino,1,2,4-Triazole</td>
<td>140 kgs</td>
<td>145 kgs</td>
</tr>
<tr>
<td>HCL</td>
<td>60 kgs</td>
<td>60 kgs</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>1100 lts</td>
<td>100+800 lts</td>
</tr>
<tr>
<td>M.D.C</td>
<td>1000 lts</td>
<td>100+800 lts</td>
</tr>
<tr>
<td>D.M Water</td>
<td>1000 lts</td>
<td>100+950 lts</td>
</tr>
<tr>
<td>Ice blocks</td>
<td>12 no’s</td>
<td>11 no’s</td>
</tr>
</tbody>
</table>
- Charge 1000 lts of 4-Amino 1,2,4-Trizole at 258-30°C in SSR-207/SSRN-205
- Charge 1000 lts of Acetourtirle in SSRN207/SSRN205
- Maintain the R.M. for 2 hrs at 25-30°C
- Heat the RM temperature to 76-80°C (Reflux)
- Maintain the RM under reflux at 76-80°C for 26 hours
- Send a sample RM to QC for TLC Check.
  (Limit = Acetyl Compound NMT 0.5%)
- If reaction is not complete, Maintain the RM under Reflux at 76-80°C for 2
  hours and recheck TLC.
- If reaction is complete, cool the RM to 5-10°C
- Maintain the RM for 30 min at 5-10°C

**Centrifugation:**
- Centrifuge the material in centrifuge CF - 202.
- Wash the material with 100 lts of chilled acetorutilne.

**METHODOLOGY FOR FLUCONAZOLE –II**

<table>
<thead>
<tr>
<th>Material</th>
<th>STD.QTY</th>
<th>ACTUAL.QTY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitrite</td>
<td>280 kgs</td>
<td>327 kgs wet</td>
</tr>
<tr>
<td>Ammonia Solution</td>
<td>75 kgs</td>
<td>71.5 kgs</td>
</tr>
<tr>
<td>HCl</td>
<td>160 kgs</td>
<td>140 kgs</td>
</tr>
<tr>
<td>D.M water</td>
<td>1110 lts</td>
<td>970+140 lts</td>
</tr>
</tbody>
</table>

- Charge 200kgs of HCl at 25-30°C in GLR -208
- Stir for dissolution (Solution should be clear)
- Cool the solution to 10-15°C
- Simultaneously Prepare a solution of sodium nitrate by dissolving 75 kg
  of Sodium nitrite in 230 ltrs of DM water in two HDPE drums.
- Add slowly the sodium nitrite solution over a period of 4-5 hrs at 10-15°C
- Spin dry the wet cake for 1 hour
- Stop the centrifuge and unload the wet cake in double poly bag need
- Label the container with detailed of product
  Batch no. etc., Wet weight = 341 kgs.

**Drying:**
- Load the wet material into TD_101.
- Dry the wet material at 85-90°C
- Record the temperature for every 60 min
- Send a sample to QC for determination of LOD initially after 4 hours.
- Stop the dryer and unload the material in to clean double poly bag lined contains
- Load the wet material into TD_101.
- Dry the wet material at 85-90°C
- Record the temperature for every 60 min
- Send a sample to QC for determination of LOD initially after 4 hours.
- Stop the dryer and unload the material in to clean double polybag containers.

**Charge 1000lts of 4NAmino 1,2,4NTrizole at 258-30°C in SSRN207/SSRN205**

**Maintain the R.M. for 2 hrs at 25-30°C**

**Heat the RM temperature to 76-80°C (Reflux)**

**Maintain the RM under reflux at 76-80°C for 26 hours**

**Send a sample RM to QC for TLC Check.**

**(Limit = Acetyl Compound NMT 0.5%)**

**If reaction is not complete, Maintain the RM under Reflux at 76-80°C for 2**

**hours and recheck TLC.**

**If reaction is complete, cool the RM to 5-10°C**

**Maintain the RM for 30 min at 5-10°C**

**Centrifugation:**

- Centrifuge the material in centrifuge CF - 202.
- Wash the material with 100 lts of chilled acetorutilne.

**METHODOLOGY FOR FLUCONAZOLE –II**

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<tr>
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</tr>
<tr>
<td>HCl</td>
<td>160 kgs</td>
<td>140 kgs</td>
</tr>
<tr>
<td>D.M water</td>
<td>1110 lts</td>
<td>970+140 lts</td>
</tr>
</tbody>
</table>

- Charge 200kgs of HCl at 25-30°C in GLR -208
- Stir for dissolution (Solution should be clear)
- Cool the solution to 10-15°C
- Simultaneously Prepare a solution of sodium nitrate by dissolving 75 kg
  of Sodium nitrite in 230 ltrs of DM water in two HDPE drums.
- Add slowly the sodium nitrite solution over a period of 4-5 hrs at 10-15°C
- Spin dry the wet cake for 1 hour
- Stop the centrifuge and unload the wet cake in double poly bag need
- Label the container with detailed of product
  Batch no. etc., Wet weight = 341 kgs.

**Drying:**

- Load the wet material into TD_101.
- Dry the wet material at 85-90°C
- Record the temperature for every 60 min
- Send a sample to QC for determination of LOD initially after 4 hours.
- Stop the dryer and unload the material in to clean double poly bag lined contains
- Load the wet material into TD_101.
- Dry the wet material at 85-90°C
- Record the temperature for every 60 min
- Send a sample to QC for determination of LOD initially after 4 hours.
- Stop the dryer and unload the material in to clean double polybag containers.
Adjust the $pH$ of RM to 8.0 – 8.5 with Ammonia solution at 20-25°C
Maintain the RM for 30 minutes at 20-25°C
Cool the RM To 10-15°C
Maintain the RM to 10-15°C

Centrifugation:
1. Centrifugation the material in centrifuge ef – 203.
2. Wash the material with 100 the of DM Water
3. Spin dry the wet cake 1 hour
4. Stop the centrifuge and unload there wet cake in double poly bag lined fiber drums
5. Label the contain with details of product Batch No.

METHODOLOGY FOR FLUCONAZOLE – III

<table>
<thead>
<tr>
<th></th>
<th>Std Qty</th>
<th>Actual Qty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caustic Potash Flakes</td>
<td>-</td>
<td>150 kgs</td>
</tr>
<tr>
<td>Atric acid</td>
<td>-</td>
<td>5 kgs</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>-</td>
<td>60 lts</td>
</tr>
<tr>
<td>Acetone</td>
<td>-</td>
<td>40 lts</td>
</tr>
<tr>
<td>Toluene</td>
<td>-</td>
<td>750 lts</td>
</tr>
<tr>
<td>Methanol</td>
<td>-</td>
<td>750 lts</td>
</tr>
<tr>
<td>Hcl</td>
<td>-</td>
<td>5 lts</td>
</tr>
<tr>
<td>DM water</td>
<td>-</td>
<td>2200 lts</td>
</tr>
</tbody>
</table>

Processing:
1. Charge 1260 lts of DM Water and 150kg of C.P. Flakes at 25-30°C in SSR.
4. Rise the RM Temperature to 60°C – 65°C
5. Maintain the RM for 24hrs at 60-65°C
6. Send a sample of RM to QC for TLC Check. (Limit : Epoxy compound NMT0.5%) If Reaction is not complete, Maintain for 2hrs more and recheck TLC.
7. If Reaction is complete cool the RM to 25-30°C
9. Adjust the $pH$ of RM to 10.0 – 10.5 with Dil Hcl (1:1) at 25-30°C
10. Stir for 30min at 25-30°C
11. Cool RM to 0-5°C
12. Maintain the RM for 4hrs at 0-5°C

Centrifugation:
6. Record the wet weight of the FL-II.
   Wet Weight = 253 kgs.

Drying:
1. Load the Wet material in to TD -101
2. Dry the wet material 55-60°C
3. Record the temperature every 60minutes.
4. Send a sample to QC for determination of LOD initially, after 12 hours and then after every 2 hours till % of LOD comes below the limit (NMT 0.5%, W/W).
5. Stop the dryer and unload the material in the clean double poly bag lined contained.
   Dry weight = 216 kgs.
1. Centrifuge the material in centrifuge CFN-203.
2. Wash the material with 200 lts of DM Water.
3. Spin Dry the wet cake for 1 hour.
4. Stop the centrifuge and unload the wet cake in double poly bag lined fiber drums.
5. Label the container with details of product Batch No. etc.
6. Record the net weight of the material net weight = 256 kgs.

**Processing**
1. Charge 400 lts of DM water at 25-30\(^\circ\)C in SSRN 211.
2. Charge net material at 25-30\(^\circ\)C in SSRN211.
3. Charge 60 lts of Ethyl acetate, 40 lts of Acetone, 5 lts of methanol not at 25-30\(^\circ\)C in SSRN-211.
4. Charge 5 kg of citric avid at 25-30\(^\circ\)C in SSRN-211.

**Drying:**
1. Load the wet material into TDN-202.
2. Dry the wet material at 85-90\(^\circ\)C.
3. Record the temperature for every 60 minutes.
4. Send a sample to Qc for determination of LOD initially, after 8 hours and then after every 2 hrs fill % of LOD comes below the limit (NMT 0.5% w/w).
5. Stop the dryer and unload the material into clean double polybag lined containers.

**Expected yield = 160-170 kgs.**

**METHODOLOGY FOR FLUCONZOL FINAL**

<table>
<thead>
<tr>
<th></th>
<th>Std Qty</th>
<th>Actual Qty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>180 kg</td>
<td>176 kg</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>8 kg</td>
<td>7 kg</td>
</tr>
<tr>
<td>Acetone</td>
<td>60 lts</td>
<td>70 lts</td>
</tr>
<tr>
<td>Toluene</td>
<td>200 lts</td>
<td>300 lts</td>
</tr>
<tr>
<td>Methanol</td>
<td>5 lts</td>
<td>5 lts</td>
</tr>
<tr>
<td>HCL</td>
<td>400 lts</td>
<td>300 lts</td>
</tr>
<tr>
<td>EDTA</td>
<td>3 kg</td>
<td>3 kg</td>
</tr>
<tr>
<td>Ammonia solution</td>
<td>120 kgs</td>
<td>4 kgs</td>
</tr>
<tr>
<td>D.M water</td>
<td>800 lts</td>
<td>350 lts</td>
</tr>
</tbody>
</table>
Processing:
1. Charge 425 lts of DM water and wet material at 25-30°C in GLR-202
2. Charge 150 kg of HCL at 25-30°C in GLR-202
3. Stir for 15min at 25-30°C
5. Stir for 30minutes and settle for 30 min.
6. Separate the aqueous layer in GLR
7. Charge 100lts of toluene at 25-30°C in GLR-208
8. Still for 30minutes and settle for 30minutes
9. Separate the aqueous layer in GLR-2002, Unload the Organic layer into drums
10. Charging 100lts of MDC in GLR-202
11. Stir for the 30minutes and settle for 30minutes
12. Separate the Organic layer and unloading into drums
13. Charge of 100lts of MDC in GLR-202
14. Stir for 30minutes separate the Organic layer
15. Charge 100 lts of MDC in GLR-202
16. Charge 100lts of MDC in GLR-202
17. Stir for 30 minutes and settle for 30 minutes
18. Separate the Organic layer and unloading into drums
19. Heat the agues layer to 45-50°C In GLR - 202
20. Maintain the RM for 15 minutes at 45 – 50°C
21. Transfer the RM into SSR-103
22. Charge the 8kg of activated Carbon into RM at 45°C
23. Stir the RM for 30minutes at 45°C
24. 50lts of DM water to Carbon bed in LF – 202 and transfer clear filtrate to the reactor GLR -301
25. Cool the aqueous layer to 25°C
26. Charge 60lts of acetone into SSR -204
27. Charge 60lts of ethyl estate into SSR – 204
28. Charge the 5 lts for methanol into SSR -204
29. Charges Citric acid + EDTA Solution into SSR -202
30. Charge the above solution in GLR -301 through MF -201 at 25°C
31. Stir the RM for 50 minutes at 25°C
32. Adjust the pH is 7.02,7.5 with 20kg of Ammonia Solution at 25-35°C
33. Send the Sample to QC

Centrifugation:
1. Centrifuge the material in centrifuge CF – 301
2. Wash the material with 60lts of DM water
3. Slurry the wet cake with 20lts of DM Water
4. Wash wet Cake with 60lts of DM water
5. Send the sample to QC for solubility of Cake in chloroform.
6. If complies spin dry the wet cake for 60minutes
7. Stop the centrifuge and unload the wet cake in double poly bag lined fiber drums and then record the weight of fluconazole

Drying:
1. Load the wet material into V.T.D -301
2. Dry the wet material at 85 to 90°C
3. Record the Temperature at 60°C
4. Sand the Sample to QC for the determination of LOD (NMT-0.5% W/W)
5. Stop the dryer unload the material into clean double ploy bag lined containers
### RESULTS AND DISCUSSION

<table>
<thead>
<tr>
<th>S.No</th>
<th>Tests</th>
<th>Specifications</th>
<th>Results of Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FL –II04001</td>
<td>FL –II04002</td>
</tr>
<tr>
<td>1.</td>
<td>Description</td>
<td>A pale of yellow to off white crystalline powder</td>
<td>Almost white Crystalline powder</td>
</tr>
<tr>
<td>2.</td>
<td>Solubility</td>
<td>Freely Soluble in Methanol</td>
<td>Complies</td>
</tr>
<tr>
<td>3.</td>
<td>Loss on</td>
<td>NMT : 0.50% w/w</td>
<td>0.30% w/w</td>
</tr>
<tr>
<td></td>
<td>Drying</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Melting Range</td>
<td>130(^\circ)C to 136(^\circ)C</td>
<td>132.3(^\circ)C – 134(^\circ)C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S. No</th>
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<th>Specification</th>
<th>Results of Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FL04001</td>
<td>FL04002</td>
</tr>
<tr>
<td>1.</td>
<td>Description</td>
<td>White crystalline powder</td>
<td>White fine crystalline powder</td>
</tr>
<tr>
<td>2.</td>
<td>Solubility</td>
<td>Slightly soluble in water, freely soluble in Methanol</td>
<td>Complies</td>
</tr>
<tr>
<td>3.</td>
<td>Identification</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Test I(By IR)</td>
<td>The IR spectrum should be Concordant with reference standard Sample</td>
<td>Complies</td>
</tr>
</tbody>
</table>
b. Test II (Melting range)  
<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>136.0</th>
<th>137.2</th>
<th>137.5</th>
<th>137.6</th>
<th>139.3</th>
<th>139.4</th>
<th>139.5</th>
</tr>
</thead>
</table>


C. Test III (TLC) 
The principle spot in the chromatogram obtained with the test solution is similar in position and size to the principle spot in the chromatogram obtained with reference solution A. 

<table>
<thead>
<tr>
<th>Test II (Melting range)</th>
<th>136.0°C to 140.0°C</th>
<th>137.2°C</th>
<th>137.5°C</th>
<th>137.6°C</th>
<th>139.3°C</th>
<th>139.4°C</th>
<th>139.5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear and colourless</td>
<td>Complies</td>
<td>Complies</td>
<td>Complies</td>
<td>Complies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


4. Appearance of the solution 

<table>
<thead>
<tr>
<th>Imp B (in house)</th>
<th>NMT 0.20%</th>
<th>---</th>
<th>---</th>
<th>---</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any other IMP</td>
<td>NMT 0.10%</td>
<td>0.04%</td>
<td>0.04%</td>
<td>0.08%</td>
</tr>
<tr>
<td>Total Impurity</td>
<td>NMT 0.50%</td>
<td>0.20%</td>
<td>0.28%</td>
<td>0.26%</td>
</tr>
</tbody>
</table>

5. Sluphated Ash 
NMT 0.10%  

6. Assay by chemical (On dryings) 
99.00% to 101.00%  

7. Residual Solvents 

<table>
<thead>
<tr>
<th>Solvent</th>
<th>NMT ppm</th>
<th>BDL</th>
<th>BDL</th>
<th>BDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanly</td>
<td>NMT 200 ppm</td>
<td>BDL</td>
<td>BDL</td>
<td>BDL</td>
</tr>
<tr>
<td>Aceton</td>
<td>NMT 200 ppm</td>
<td>BDL</td>
<td>BDL</td>
<td>BDL</td>
</tr>
<tr>
<td>Methyl dichloride</td>
<td>NMT 600 ppm</td>
<td>BDL</td>
<td>BDL</td>
<td>BDL</td>
</tr>
<tr>
<td>Ethyl Acetone</td>
<td>NMT 500 ppm</td>
<td>100 ppm</td>
<td>90 ppm</td>
<td>80 ppm</td>
</tr>
<tr>
<td>Tolune</td>
<td>NMT 500 ppm</td>
<td>200 ppm</td>
<td>158 ppm</td>
<td>169 ppm</td>
</tr>
</tbody>
</table>
CONCLUSION

Three batches of Fluconazole Crude are FL-II04002 and FL-11104003 and Fluconazole Final are FL04001, FL04002 and FL 04003 are taken for performing prospective validation of the process.

All the Critical process Parameters and In-process results were well within the approved standard parameters and limits.

All the Quality Attributes of Intermediate and Finished API are very well within the already established approved specified limit.

Manufacturing facility (Critical Instruments, utilities) and other support system were checked for their functionality and found ok.

Fluconazole, when manufactured by using the approved Master production and control records, Produces a consistent quality of the product. All the three batches were found within the specifications by following predetermined Critical Process Parameters, Inprocess Tests and by Raw materials and Intermediates of Specified quantity.

Therefore, the process for manufacturing Fluconazole considered to be validated prospectively.

REFERENCES

5. P.P. Sharma, Practice GMPs.
6. P.P. Sharma, Practice of GMPs.
9. WWW.rxlist.com