

<b>VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center</b>		Issue Date: 12 Aug 2014	Document: <b>MR-590.01</b>
Authorized by: <b>Jan Hickey CHIEF, CMS</b>		Version: <b>1</b>	Page 1 of 8
Sub Authorizer: <b>Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION</b>			
Document Title: <b>Manufacture of 300 mg Lithium ER PLACEBO</b> Tablets, 51 - 94 Kgs			
<b>INVALID 2 WKS FROM PRINT DATE</b>		Print Date: <b>7/27/15</b>	

### MANUFACTURING PROCEDURES

<b>CSP 590</b>	<b>Production Run (Batch/Lot) #:</b> _____	<b>Theoretical Lot Size<sup>1</sup>:</b> _____ kg/batch	<b>Start Time:</b> _____ <b>Start Date:</b> _____
<b>MPR #:</b> _____	<b>TID #:</b> _____	<b>Theoretical # units/batch<sup>2</sup>:</b> _____	<b>End Time:</b> _____ <b>End Date:</b> _____

<sup>1</sup>Batch size to be determined at time of manufacture (Procedures suitable for 51-94 kg batches)

<sup>2</sup>Theoretical No. of Tablets to be calculated at time of production (Batch size x 1,000,000/weight of target dosage form)

### Component ID, Weights and Measures Log

COMPONENT	TID	EXPIRATION DATE	QUANTITY PER TABLET	FORMULA =	BULK QTY REQUIRED	QUANTITY ON HAND	CALC. PERFORMED BY	CALC. CHECKED BY	QM CHECK
Avicel PH 302 (98.5%)			369.4 mg	0.985 x batch size (kg) =	_____ kg	_____ kg			
Cab-O-Sil M5P (1.0%)			3.8 mg	0.01 x batch size (kg) x 1,000 =	_____ g	_____ g			
Magnesium Stearate (0.5%)			1.9 mg	0.005 x batch size (kg) x 1,000 =	_____ g	_____ g			


\*Target tablet weight = 375mg

Use tablet tooling: Debossed punch #137583; opposite punch #91380; die #80380

Step #:	Procedure Description	Specification – Tolerances	Value	Performed By:	Checked By:
	<b>Safety Precautions: Normal personal protective gear. Ear protection recommended. No special safety precautions required.</b>				

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Authorized by: <b>Jan Hickey CHIEF, CMS</b>	Version: <b>1</b>	Page 2 of 8
Sub Authorizer: <b>Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION</b>		
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1A	Set up tablet press with the correct tooling.	<i>Debossed punch #137583</i>  <i>Opposite punch #91380</i>  <i>Die #80380</i>			
1-B	Manually verify the calibration of each balance to be used with a set of certified masses prior to weighing active ingredient or excipients. <ul style="list-style-type: none"> <li>Only use scales calibrated for the unit of measure to be weighed <ul style="list-style-type: none"> <li>i.e. Kg scale for Kg weight,</li> <li>mg scale for mg weight,</li> <li>g scale for g weight.</li> </ul> </li> <li>Use one certified mass for each scale that weighs less than the lowest value to be weighed on that scale.</li> <li>Use one certified mass for each scale that weighs more than the heaviest value to be weighed on that scale.</li> <li>Attach a printout of the results to this page.</li> <li>Actual results shall fall within <math>\pm 0.5\%</math> of the test mass.</li> </ul>	Mettler Toledo No. _____  Certified Low Mass Weight: _____g  Certified High Mass Weight: _____g	Low Mass Range:  Low: _____ g High: _____ g Actual: _____ g High Mass Range:  Low: _____ g High: _____ g Actual: _____ g		
1B con- tin- ued		Floor Scale _____  No. _____  Certified Mass Weight: _____mg	Mass Range $\pm 0.5\%$ of the test mass:  Low: _____mg High: _____mg Actual: _____mg		

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Authorized by: <b>Jan Hickey CHIEF, CMS</b>		Version: <b>1</b>	Page 3 of 8
Sub Authorizer: <b>Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION</b>			
Document Title: <b>Manufacture of 300 mg Lithium ER PLACEBO</b> Tablets, 51 - 94 Kgs			
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1B con- tin- ued		Floor Scale _____  No. _____  Certified Mass Weight:  _____mg	Mass Range $\pm$ 0.5% of the test mass:  Low: _____mg  High: _____mg  Actual: _____mg		
2	Weigh target amount of _____kg of Avicel PH 302 powder and record actual weight.  Acceptable range $\pm$ 0.1 kg of the bulk quantity determined in the Component ID, Weights and Measures Log	Minimum : _____kg To  Maximum: _____kg	<b>ACTUAL WEIGHT OF AVICEL PH 302:</b>  _____kg		
3	Weigh target amount of _____g of Cab-O-Sil M5P and record actual weight.  Acceptable range $\pm$ 1% of the bulk quantity determined in the Component ID, Weights and Measures Log (target x 0.99 min; target x 1.01 max)	Minimum : _____g To  Maximum: _____g	<b>ACTUAL WEIGHT OF CAB-O-SIL M5P:</b>  _____g		

VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center		Issue Date: 12 Aug 2014	Document: <b>MR-590.01</b>
Authorized by: <b>Jan Hickey CHIEF, CMS</b>		Version: <b>1</b>	Page 4 of 8
Sub Authorizer: <b>Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION</b>			
Document Title: <b>Manufacture of 300 mg Lithium ER PLACEBO</b> Tablets, 51 - 94 Kgs			
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4	Place powders from steps 2 and 3 in the <b>10 cubic foot ribbon blender</b> .  Mix powders for 10 minutes.	Required mix time $\geq$ 10 minutes	Start Time: _____  Stop Time: _____  Total mixing time: _____min		
5	Sieve magnesium stearate through a 40-mesh screen.  Weigh target amount of _____g of sieved magnesium stearate and record actual weight.  Acceptable range: $\pm$ 1% of the bulk quantity determined in the Component ID, Weights and Measures Log (target x 0.99 min; target x 1.01 max)	Minimum : _____g  To  Maximum: _____g	<b>ACTUAL WEIGHT OF MAGNESIUM STEARATE:</b>  _____g		
6	Add the magnesium stearate to the blender.  Mix with the powder blend for 5 minutes.	Required mix time between 4.5 and 5.5 minutes	Start Time: _____  Stop Time: _____  Total mixing time: _____min.		
7	Empty the powder blend from the mixer.  Record the weight of the powder.		<b>WEIGHT OF POWDER BLEND:</b>  _____ kg (A)		

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Authorized by: <b>Jan Hickey CHIEF, CMS</b>	Version: <b>1</b>	Page 5 of 8
Sub Authorizer: <b>Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION</b>		
Document Title: <b>Manufacture of 300 mg Lithium ER PLACEBO Tablets, 51 - 94 Kgs</b>		
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8	Transfer the powder blend to the hopper of the tablet press.  Rotate the die table manually at least 3 full revolutions.  Collect 10 tablets and determine the average tablet weight.	<i>Set up specification</i>  Average tablet weight (375 mg) $\pm$ 3%: 363.8 – 386.3 mg	Weight of 10 Tablets:  _____mg  Ave. Tablet Weight:  _____mg (weight of 10 tablets $\div$ 10)		
9	Adjust tablet weight as necessary and repeat step 8 until the average tablet weight is within the set up specification.	Average tablet weight (375 mg) $\pm$ 3%: 363.8 – 386.3 mg	Weight of 10 Tablets:  _____mg  Ave. Tablet Weight:  _____mg (weight of 10 tablets $\div$ 10)		
10	Adjust tablet compression until the average thickness and hardness of 10 tablets are within the set up specifications.  Note: Tablet thickness should be measured at the center of the tablet.  If capsule Weight, Thickness and Hardness are acceptable, record tablet hardness and proceed to step 12 Sotax AT4 Set-up.  Attach copies of all weight and thickness tapes taken to MR.	<i>Set up specification</i> Average tablet thickness (4.65 mm) $\pm$ 1%: 4.6 – 4.7 mm  <i>Set up specification</i> Tablet hardness: 6 Kp - 40 Kp	Average Tablet Thickness:  _____mm  Tablet hardness:  _____Kp		
11	Set aside all in-process machine set up materials.				

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Authorized by: <b>Jan Hickey CHIEF, CMS</b>	Version: <b>1</b>	Page 6 of 8
Sub Authorizer: <b>Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION</b>		
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12	<b>Sotax AT4 Setup:</b>  Set up the Sotax AT4 with the acceptable limits using the <i>In process specifications</i> .  Tablet weight nominal value..... = <u>375</u> mg <ul style="list-style-type: none"> <li>○ T1 limit = 2%</li> <li>○ T2 limit = 3%</li> <li>○ PL limit <math>\geq</math> 50%</li> </ul> Tablet thickness nominal value. = <u>4.65</u> mm <ul style="list-style-type: none"> <li>○ T1 limit = 1%</li> <li>○ T2 limit = 2%</li> <li>○ PL limit <math>\geq</math> 50%</li> </ul> Tablet hardness nominal value. 28 Kp <ul style="list-style-type: none"> <li>○ T1 limit = 13 - 33 Kp</li> <li>○ T2 limit = 6 - 40Kp</li> <li>○ -PL limit <math>\leq</math> 5Kp</li> <li>○ +PL limit <math>\geq</math> 50Kp</li> </ul>	<i><b>In process specifications</b></i>  Average tablet weight T1: 375 mg $\pm$ 2%: <b>367.5 – 382.5 mg</b>  T2: 375 mg $\pm$ 3% <b>363.8 – 386.3 mg</b>  Average tablet thickness T1: 4.65mm $\pm$ 1% <b>4.6 – 4.7 mm</b>  T2: 4.65 mm $\pm$ 2%: <b>4.56 – 4.74 mm</b>  Tablet hardness: <b>T1: 13 – 33 Kp</b> <b>T2: 6 – 40 Kp</b>			

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Authorized by: <b>Jan Hickey CHIEF, CMS</b>		Version: <b>1</b>	Page 7 of 8
Sub Authorizer: <b>Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION</b>			
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13	<p>Once the machinery produces tablets within the set up specification, operate the:</p> <ul style="list-style-type: none"> <li>Tablet press in the automated continuous mode,</li> <li>AT4 and its Stand Alone Diverter (SAD) to sample 10 tablets at 10 minute intervals to measure each tablets weight, thickness, and hardness.</li> </ul> <p>Collect tablets in a sanitary plastic bag.</p> <p>Refill powder hopper as needed.</p> <p>If necessary, make adjustments to the machinery to produce tablets within the in process specifications. Record all process changes.</p> <p>Continue production until the majority of available powder has been tableted or the desired number of tablets has been produced.</p>				
14	<p>After tablet production ends, weigh the finished tablets.</p> <p>Record the weight of the finished tablets.</p>		<p><b>WEIGHT OF TABLETS PRODUCED:</b></p> <p>_____ kg (B)</p>		
15	<p>Remove remaining powder from the tablet press and collect in a container.</p> <p>Weigh the remaining powder and record actual weight below.</p>		<p><b>WEIGHT OF REMAINING POWDER:</b></p> <p>_____ g (C)</p>		

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Authorized by: <b>Jan Hickey CHIEF, CMS</b>	Version: <b>1</b>	Page 8 of 8
Sub Authorizer: <b>Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION</b>		
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16	<p>Calculate a percent yield based on the number of tablets produced.</p> <p>Actual:</p> <p>i. Calculate the average tablet weight from in-process testing</p> $= \frac{\sum \text{Individual tablet weights}}{\text{Total number of tablets weighed}} = \text{_____ } mg(D)$ <p>ii. Estimate the total number of tablets produced</p> $= \frac{\text{_____ } kg(B) \times 1,000,000}{\text{_____ } mg(D)} = \text{_____ } (E)$ <p>Theoretical number of tablets:</p> $= \frac{([\text{_____ } kg(A) \times 1,000] - \text{_____ } g(C))}{0.375g}$ $= \text{_____ } (F)$	<p>Acceptable range:</p> <p>75-105% of theoretical</p>	<p><b>PERCENT YIELD =</b></p> $= \frac{\text{_____ } (E)}{\text{_____ } (F)} \times 100$ $= \text{_____ } \%$		
17	Double bag and quarantine tablets until released by QCS.				
18	Enter final inventory in DOSE and La Puerta				