

VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center		Issue Date: 25 Aug 2014	Document: MR-574.04
Document Owner: Jan Hickey CHIEF, CMS		Version: 2	Page 1 of 27
Approved by: Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION			
Document Title: : Over-Encapsulation of Placebo Tablet for Methylprednisolone 4mg using the Capsugel Ultra 8II			
INVALID 2 WKS FROM PRINT DATE		Print Date: 7/27/15	

MANUFACTURING PROCEDURES

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

¹Batch size to be determined at time of manufacture

²Theoretical No. of Units to be calculated at time of production (see 'bulk quantity required' for capsules in Component ID, Weights and Measures Log section)

Component ID, Weights and Measures Log

COMPONENT	TID	EXPIRATION DATE	QUANTITY PER CAPSULE	FORMULA =	BULK QTY REQUIRED	QUANTITY ON HAND	CALC. PERFORMED BY	CALC. CHECKED BY	QM CHECK
Methylprednisolone PLACEBO tablet			1 tablet	Batch size x 1 cap/tab =	_____ tabs	_____ tabs			
Avicel PH 302			200 mg	Batch size x 0.2g/cap x 1.3* =	_____ g	_____ g			
Capsules (size '1' blue opaque)			1	Batch size x 1 cap/cap =	_____ caps	_____ caps			

*Includes 30% overage of backfill material

Target weight = to be determined during production run

Step #:	Procedure Description	Specifications-Tolerances	Value	Performed By:	Checked By:
	Safety Precautions: No special safety precautions. Ear protection recommended				

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1	<p>Manually verify the calibration of each balance to be used with a set of certified masses prior to weighing active ingredient or excipients.</p> <ul style="list-style-type: none"> • Only use scales calibrated for the unit of measure to be weighed <ul style="list-style-type: none"> ○ i.e. Kg scale for Kg weight, ○ mg scale for mg weight, ○ g scale for g weight. • Use one certified mass for each scale that weighs less than the lowest value to be weighed on that scale. • Use one certified mass for each scale that weighs more than the heaviest value to be weighed on that scale. • Attach printer tape (if available). • Actual results shall fall within $\pm 0.5\%$ of the test mass. 	<p>Mettler Toledo No. _____</p> <p>Low Mass : _____g</p> <p>High Mass: _____g</p>	<p>Low Mass Range:</p> <p>Low: _____g</p> <p>High: _____g</p> <p>Actual: _____g</p> <p>High Mass Range:</p> <p>Low: _____g</p> <p>High: _____g</p> <p>Actual: _____g</p>		
		<p>Sartorius No. _____</p> <p>Low Mass: _____mg</p> <p>High Mass: _____mg</p>	<p>Low Mass Range:</p> <p>Low: _____mg</p> <p>High: _____mg</p> <p>Actual: _____mg</p> <p>High Mass Range:</p> <p>Low: _____mg</p> <p>High: _____mg</p> <p>Actual: _____mg</p>		

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2	Weigh approximately _____ g of Avicel PH 302. Record this weight. Attach printer tape (if available) to this page. Acceptable range $\pm 1\%$ of bulk quantity determined in the Component ID, Weights and Measures Log Minimum value _____ = target x 0.99 Maximum value _____ = target x 1.01	Minimum: _____g Maximum: _____g	Weight of Avicel PH302 _____g		
3	Weigh 10 empty size 1 capsules. Record the total weight. Attach printer tape (if available) to this page.		Weight of 10 capsules: _____mg		
4	Calculate the average weight of one empty capsule. (Actual weight of 10 capsules from step 3 divided by 10)		Average capsule weight: _____mg		
5	Weigh 10 Methylprednisolone PLACEBO tablets. Record the total weight. Attach printer tape (if available) to this page.		Weight of 10 Methylprednisolone PLACEBO tablets: _____mg		
6	Calculate the average weight of one Methylprednisolone PLACEBO tablet (Actual weight of 10 tablets from step 5 divided by 10)		Average Methylprednisolone PLACEBO tablet weight: _____mg		

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7	<p>Calculate the target weight (in mg) of the finished capsule.</p> <p>Average weight of 1 empty capsule (step 4) + average weight of Methylprednisolone PLACEBO tablet (step 6) + 200 mg (amount of Avicel PH 302/capsule)</p> <p>Step 4 _____mg + Step 6 _____mg + 200 mg = _____mg</p>		<p>Target weight of finished capsule:</p> <p>_____mg</p>		
8	<p>Calculate the acceptable range (in mg) for the weight of finished capsules.</p> <p>Target weight of finished capsule (step 7) ± 15%</p> <p>Minimum value = target x 0.85</p> <p>Maximum value = target x 1.15</p>	<p>FINAL SPEC</p> <p>Minimum:</p> <p>_____mg</p> <p>Maximum:</p> <p>_____mg</p>			
9	<p>With the Ultra 8 II set up for size 1 capsules,</p> <p>Set the Ultra 8 II to the lowest fill weight by:</p> <ul style="list-style-type: none"> • Increasing the rotary table speed, • Increasing the auger speed, and • Set the machine to 2 revolutions of the rotary body ring. 				

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Step #:	Procedure Description	Specifications-Tolerances	Value	Performed By:	Checked By:
10	<p>Place capsules in the capsule hopper and add Avicel PH-302 to product hopper.</p> <p>Capsule Load/Separation:</p> <ul style="list-style-type: none"> • Place an empty capsule Fill Ring on the Carrier Ring and turn it clockwise until it stops firmly against the Carrier Ring Lug. • Make sure the Gate Lifter Pin is pushed in. • Turn the power on at the Main Disconnect and pull out the Emergency Stop button. • Depress the Vacuum Pump and Hydraulic Pump buttons. • Turn the Rectifier Jog/Run switch to the Run position. • Turn the Rectifier Auto/Manual switch to Auto. • Set Rectifier RPM to 100. • Depress the Rectifier Start button. <p>With the capsule rectifier set to Run, the automatic Ring Spinner will turn the Ring Carrier counter-clockwise, which is necessary to assure the capsules are fully separated.</p> <ul style="list-style-type: none"> • Press the Rectifier start button. The Ring Spinner will rotate and the Capsule Rectifier will fill the Fill Ring with empty capsules. • Remove the capsule Fill Ring from the Carrier Ring being careful to hold it horizontally to avoid spilling capsules. <p>Place Carrier Ring on a table and remove the top (cap) Fill Ring being careful to avoid spilling capsules.</p>				

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Step #:	Procedure Description	Specifications-Tolerances	Value	Performed By:	Checked By:
11	<p>Loading tablets into capsule:</p> <ul style="list-style-type: none"> • Manually fill the Over-encapsulation (OE) Ring with Methylprednisolone PLACEBO tablets • Position the OE Ring over the filled Capsule Body Fill Ring • Squeeze the mechanism opening the OE Ring which fills each empty capsule body with 1 Methylprednisolone PLACEBO tablet. • Verify that all capsules contain 1 Methylprednisolone PLACEBO tablet 				
12	<p>Filling Powder into Capsules:</p> <p>Fill the capsule bodies with Avicel PH-302 by:</p> <ul style="list-style-type: none"> • Placing the capsule body Fill Ring onto the rotary table • Rotating the body Fill Ring on the rotary table counter clockwise until the Fill Ring is stopped by the lug. • Pressing the rotary table button which automatically shifts the drug hopper into position over the body Fill Ring filling the capsules with powder. <ul style="list-style-type: none"> ○ After the rotary table rotates the set number of revolutions, the drug hopper will shift back to the rest position. • Use a plastic scraper to remove excess fill from the top of the Fill Ring. 				

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Step #:	Procedure Description	Specifications-Tolerances	Value	Performed By:	Checked By:
13	<p>Capsule closing, locking and dumping:</p> <p>Rejoin the capsule bodies and caps by placing the Cap Fill Ring onto the Body Fill Ring making sure the large and small lugs match.</p> <p>Place the Body and Cap Fill Rings on the Peg Ring of the closing station.</p> <p>Push the closing station in.</p> <p>After closure has taken place, pull the closing station back out.</p> <p>Turn the ring clamp clockwise to hold the Fill Rings in place.</p> <p>Rotate the closing station to discharge the capsules into a bucket lined with a sanitary plastic bag.</p>				
14	<p>Weigh 10 filled and closed capsules and record the weight.</p> <p>If capsule weights are acceptable, proceed to step 15 Sotax AT4 Set-up.</p> <p>If capsule fill weights do not fall within the specification limits, adjust as necessary,</p> <ul style="list-style-type: none"> • the rotary table to required number of revolutions, and/or • Feeder auger speed control, and/or • Rotary table speed control and/or • Powder fill level in hopper <p>to achieve an average capsule weight within the acceptable limits</p> <p>Repeat steps 10 – 14 until the weights fall within the specifications.</p> <p>Attach copies of all weights taken to MR.</p>		<p>Weight of 10 capsules: _____mg</p> <p>AVE. CAPSULE WEIGHT: _____mg (wt. of 10 capsules ÷ 10)</p>		

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15	<p>Sotax AT4 Setup:</p> <p>Enter the following values in the Sotax AT4 program.</p> <p>Capsule target weight</p> <ul style="list-style-type: none"> • Filled capsule weight nominal value (step 7) = _____ mg <ul style="list-style-type: none"> ○ T1 limit =10% ○ T2 limit =15% (step 7) ○ (PL) In-plausible Limit = 50% <p>Capsule length/diameter.</p> <p>Note: The capsule length/diameter is for information only. It is not a release requirement. The capsule length/diameter was obtained prior to batch manufacture by calculating the average length of 10 closed capsule measured using calibrated calipers.</p> <ul style="list-style-type: none"> • Capsule Length/Diameter: • nominal value= <u>18.90</u> mm <ul style="list-style-type: none"> ○ T1 limit =3% ○ T2 limit = 6.5% ○ (PL) In-Plausible Limit = 50% 																		
16	<p>When capsule fill weights meet the final specification and the Sotax AT4 is setup, fill the capsules.</p> <p>Sample 10 randomly selected, filled and locked capsules and run them through the Sotax AT4 tablet/capsule inspection system for in process checks based upon the tray count in the following table.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="text-align: center;">Trays/lot</td> <td style="text-align: center;">≥100</td> <td style="text-align: center;">50 – 99</td> <td style="text-align: center;">25 – 49</td> <td style="text-align: center;">5 - 24</td> <td style="text-align: center;">2 - 4</td> <td style="text-align: center;">1</td> </tr> <tr> <td style="text-align: center;">Sample every X Tray</td> <td style="text-align: center;">10</td> <td style="text-align: center;">7</td> <td style="text-align: center;">5</td> <td style="text-align: center;">4</td> <td style="text-align: center;">2</td> <td style="text-align: center;">1</td> </tr> </table> <p>Repeat filling procedures until the desired number of capsules have been manufactured, refilling powder and capsule hoppers as needed.</p>	Trays/lot	≥100	50 – 99	25 – 49	5 - 24	2 - 4	1	Sample every X Tray	10	7	5	4	2	1				
Trays/lot	≥100	50 – 99	25 – 49	5 - 24	2 - 4	1													
Sample every X Tray	10	7	5	4	2	1													

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17	Tare a container and 2 sanitary plastic bags to collect de-dusted capsules. Slowly pour the filled/locked capsules into the capsule polisher/de-duster. Record weight of container(s) when capacity is reached. Attach printer tapes if available.		Weight of finished capsules: _____ kg		
18	Print in process test results from the Sotax AT4 and attach to the batch record.				
19	Calculate a percent yield based on the number of capsules produced. A = Capsule yield, based on weight A = [Weight of finished capsules (step 17) x 1,000,000] ÷ average weight of an individual capsule (mg, from printed Sotax AT4 results page) $A = \frac{\text{_____ kg} \times 1,000,000}{\text{_____ mg}} = \text{_____}$ T = Theoretical batch size (# of capsules) = _____	Acceptable range: 80-110% of theoretical	Percent Yield: $\frac{\text{_____ (A)}}{\text{_____ (T)}} \times 100 =$ = _____ %		
20	Double bag and quarantine tablets until released by IQM.				
21	Post inventory in La Puerta.				