

VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center		Issue Date: 21 Aug 201421 Aug 2014	Document: MR-571.04
Document Owner: Jan Hickey CHIEF, CMS		Version:	Page 1 of 9
Approved by: Stanley JOHNSON CHIEF, QUALITY CONTROL SECTION			
Document Title: Filling Placebo for Clopidogrel 75 mg Tablets on the Ultra 8II Using the SotaxAT4			
INVALID 2 WKS FROM PRINT DATE		Print Date: 7/27/15	

MANUFACTURING PROCEDURES

CSP/Project #: <u>CSP571</u>	Production Run (Batch/Lot) #: _____	Theoretical # units/batch ¹ _____	Start Time: _____ Start Date: _____
MPR #: _____	TID #: _____		End Time: _____ End Date: _____

¹Theoretical No. of Units to be determined at time of production (see 'BULK QTY REQUIRED' for capsules in Component ID, Weights and Measures Log);
Procedures suitable for 3,000-10,000 capsule batches

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
Avicel PH 302			455 mg	[Batch size x 0.455g/cap x 1.5*] divided by 1,000 =	_____kg	_____kg			
Capsules (size 'AA' Swedish Orange Opaque,)			1	Batch size x 1 cap/cap =	_____caps	_____caps			

*Includes 50% overage of fill material

Step #:	Procedure Description	Specifications-Tolerances	Value	Performed By:	Checked By:
	Safety Precautions: No special safety precautions necessary				

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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. 	Mettler Toledo No. _____ Low Mass : _____g High Mass: _____g	Low Mass Range: Low: _____g High: _____g Actual: _____g High Mass Range: Low: _____g High: _____g Actual: _____g		
		Sartorius No. _____ Low Mass: _____mg High Mass: _____mg	Low Mass Range: Low: _____mg High: _____mg Actual: _____mg High Mass Range: Low: _____mg High: _____mg Actual: _____mg		

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2	<p>Weigh approximately _____ kg of Avicel PH 302.</p> <p>Record this weight. Attach printer tape (if available) to this page.</p> <p>Acceptable range \pm 1% of bulk quantity determined in the Component ID, Weights and Measures Log</p> <p>Minimum value _____ = target x 0.99</p> <p>Maximum value _____ = target x 1.01</p>	<p>Minimum:</p> <p>_____kg</p> <p>Maximum:</p> <p>_____kg</p>	<p>Weight of Avicel PH302</p> <p>_____kg</p>		
3	<p>Weigh 10 empty size AA capsules.</p> <p>Record the total weight. Attach printer tape (if available) to this page.</p>		<p>Weight of 10 capsules:</p> <p>_____mg</p>		
4	<p>Calculate the average weight of one empty capsule.</p> <p>(Actual weight of 10 capsules from step 3 divided by 10)</p>		<p>Average capsule weight:</p> <p>_____mg</p>		
5	<p>Calculate the target weight (in mg) of the finished capsule.</p> <p>Average weight of 1 empty capsule (step 4) + 455 mg (amount of Avicel PH 302/capsule)</p>		<p>Target weight of finished capsule:</p> <p>_____mg</p>		

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6	Calculate the acceptable range (in mg) for the weight of finished capsules. Target weight of finished capsule (step 5) \pm 15% Minimum value = target x 0.85 Maximum value = target x 1.15	FINAL SPEC Minimum: _____mg Maximum: _____mg			
7	With the Ultra 8 II set up for size AA capsules, Set the Ultra 8 II to the lowest fill weight by: <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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8	<p>Place capsules in the Capsule Hopper</p> <p>Add Avicel PH 302 to the Powder Hopper.</p> <p>Loading and Separating Capsules</p> <ul style="list-style-type: none"> Place an empty Fill Ring on the Carrier Ring and turn it clockwise until it stops firmly against the 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. <ul style="list-style-type: none"> The Ring Spinner will rotate and the Capsule Rectifier will fill the Carrier Ring with empty capsules. The automatic Ring Spinner will turn the Carrier Ring counter-clockwise to fully separate the capsules. Remove the Capsule Fill Ring from the Carrier Ring being careful to hold it horizontally to avoid spilling capsules. Place Carrier Ring on a table and remove the top (Cap) Ring being careful to avoid spilling capsules. 				

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9	Filling Capsules: Fill the capsule bodies with Avicel PH302 by: <ul style="list-style-type: none"> Placing the Capsule Body Ring onto the Rotary Table Rotating the Body Ring on the Rotary Table counter clockwise until the ring is stopped by the Lug. Pressing the Rotary Table button which automatically shifts the Drug Hopper into position over the Body Ring filling the capsules with powder. <p>After the Rotary Table has rotated the set number of revolutions, the Drug Hopper will shift back to the rest position.</p> <p>Use a plastic scraper to remove excess fill from the top of the ring.</p>				
10	Capsule closing, locking and dumping: <p>Rejoin the capsule bodies and caps by placing the Cap Ring onto the Body Ring making sure the large and small lugs match.</p> <p>Place the Body and Cap 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 rings in place.</p> <p>Rotate the Closing Station to dump the capsules into a bucket lined with a sanitary plastic bag.</p>				

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11	<p>Weigh 10 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 Powder Hopper <p>to achieve an average capsule weight within the acceptable limits</p> <p>Repeat steps 8-11 until the weights fall within the specifications.</p> <p>Attach copies of all weights taken to MR.</p>		<p>Weight of 10 capsules:</p> <p>_____mg</p> <p>AVE. CAPSULE WEIGHT:</p> <p>_____mg (wt. of 10 capsules ÷ 10)</p>		
12	<p>Sotax AT4 Setup:</p> <p>Using the target weight of capsule from step 5 and the average of 10 capsule lengths measured using calibrated calipers, set up the Sotax AT4 with the acceptable limits.</p> <ul style="list-style-type: none"> Filled capsule weight nominal value (step 5) = _____mg <ul style="list-style-type: none"> T1 limit =10% T2 limit =15% In-plausible limit =50% <p>Note: The capsule length/diameter is for information only. It is not a release requirement.</p> <ul style="list-style-type: none"> nominal value=_____mm <ul style="list-style-type: none"> T1 limit =3% T2 limit = 6.5% (PL) In-Plausible Limit = 50% 				

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13	<p>When capsule fill weights meet the final specification and the Sotax AT4 is setup, fill the capsules.</p> <p>At 15 minute intervals, randomly select 10 filled/locked capsules and run them through the Sotax AT4 tablet/capsule inspection system for in process checks.</p> <p>Repeat filling procedures until the desired number of capsules have been manufactured, refilling powder hopper as needed.</p>				
14	<p>Tare a container and 2 sanitary plastic bags to collect de-dusted capsules.</p> <p>Slowly pour the filled/locked capsules into the capsule polisher/de-duster.</p> <p>Record weight of container(s) when capacity is reached.</p> <p>Attach printer tapes if available.</p>		<p>Weight of finished capsules:</p> <p>_____ kg</p>		
15	Print in process test results from the Sotax AT4 and attach to the batch record.				
16	<p>Calculate a percent yield based on the number of capsules produced.</p> <p>A = Capsule yield, based on weight</p> <p>A = [Weight of finished capsules (step 14) x 1,000,000] ÷ average weight of an individual capsule (mg, from printed Sotax AT4 results page)</p> $A = \frac{\text{_____ kg} \times 1,000,000}{\text{_____ mg}} = \text{_____}$ <p>T = Theoretical batch size (# of capsules) = _____</p>	<p>Acceptable range:</p> <p>80-110% of theoretical</p>	<p>Percent Yield:</p> $\frac{\text{_____ (A)}}{\text{_____ (T)}} \times 100 =$ <p>= _____ %</p>		

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17	Double bag and quarantine tablets until released by IQM.				
18	Post inventory in La Puerta.				