

**MedPointe Product & Process Development**  
**Program Priorities & Issues**  
**September 9, 2002**



PTX0143-00001

## COMMERCIAL PRODUCT TECHNICAL SUPPORT

### ASTELIN NASAL SPRAY

Issue/Program	Priority	Critical Path	Timing	Manager <sup>1</sup>	Status/Comments
Qualify 34.5 mL V-bottom bottle	High	Launch of V-Bottom Bottle	Q4/FY03		
Generate stability data	Medium		August 02	ADD/CY	Issue report with historical stability data for manually applied spigot pumps. Historical data summary targeted for 9/13/02.
Qualify Marlex 5502BN Resin Stability program	High	Maintain Component Supply	Q3/FY03	CY/ML	Studies initiated to qualify transfer to new bottle resin. No data has been received for intermediate test points at accelerated conditions. Three month pull September 14, 2002.

### ASTELIN/STEROID COMBINATION PRODUCT

New Nasal Solution Product Combination of Azelastine HCl and an Approved Steroid	Medium	Extension Product for Lifecycle Maintenance	Ongoing	ADD/VP/GD/JH/JG	Literature search initiated to determine historical perspective and evaluate product feasibility. Initial team meeting 9/6/02. Need to evaluate market potential, patent position and development
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### DORAL TABLETS

Qualify Decatur to manufacture Doral Tablets	Medium	Maintain Commercial Tablet Supply	Q4/FY03	VP GD	PPD-01-07-Process Validation reviewed. Blending of magnesium stearate is a concern. Five cu.ft. blender recommended as solution. Project status reviewed on 8/20/02: major issues need to be resolved prior to next PV batch. Timeline needs to be revised to meet April 04 supply date. Operation has identified and requested reference standards. Methods required for recertification have been forwarded GD.
Qualification of new drug substance supplier	Medium	Maintain Drug Substance Supply	Q3/FY04	VP	Tateyama Kasei and FIS to be evaluated as suppliers of quazepam drug substance. Decatur is looking for samples of quazepam from FIS, supposedly sent June 02.

<sup>1</sup>ADD-Alex D'Addio, GD-Grace Dang, WH-Weixuan He, JH-John Higson, ML-Mary Lehr, EM-Ed Mikalsen, HM-Hank Mortko, VP-Vithal Patel, WR-Will Robinson, BR-Bryan Roeklein, CY-Cindy Yayac

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CIP2055  
 Argentum Pharmaceuticals LLC v. Cipla Ltd.  
 IPR2017-00807

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 SUBJECT TO STIPULATED PROTECTIVE ORDER**

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## COMMERCIAL PRODUCT TECHNICAL SUPPORT (continued)

### FELBATOL SUSPENSION

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Qualify Micron Technologies as approved milling site	High	Maintain Supply of Micronized Drug Substance	Q2	GD/VP	FDA approved Micron Technologies. Three month stability data on first batch and second batch required to generate final report. A report at 3 month stability of first batch 2C68 has been written and is waiting for review at PPD (due 8/6/02). Additional felbamate fine is required. MT is milling an additional order of 860kg. Milling by Orgamol is reactivated. 280 kg was already sent. Issues about protocol and validation are being discussed.

### SOMA 350

Transfer Manufacturing Process to Decatur Identify critical process parameters	Critical	Maintain Commercial Supply of Tablets	On-going	WR/HM/ JH	Work with Ray Chen to develop an experimental design that will be used to identify critical parameters in manufacturing process for SOMA 350 Tablets.
Validate specificity for USP assay	High	Response to FDA Inspection	Q3/FY03	HM	Work initiated in response to FDA 483. Updated quotations from Magellan submitted for approval. Estimated completion date – end of September 02.

### SOMA COMPOUND

Validate specificity for USP assay	High	Response to FDA Inspection	Q3/FY03	HM	Work initiated in response to FDA 483. Updated quotations from Magellan submitted for approval. Estimated completion date – end of September 02.
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### SOMA COMPOUND W/CODEINE

Validate specificity for USP assay	High	Response to FDA Inspection	Q3/FY03	HM	Work initiated in response to FDA 483. Updated quotations from Magellan submitted for approval. Estimated completion date – end of September 02.
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# PRODUCT DEVELOPMENT

## ASTELIN NASAL SPRAY

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Astelin Double-Strength – Formulation Development	High	Taste Improvement	On-going	GD/VP	Formulations with current azelastine HCl level (0.1%) thickened with HPMC or CMC have been stable for 4 months. Formulations with 0.14% azelastine HCl are stable with CMC thickener but not with extra HPMC. Formulations with 0.28% azelastine HCl and sorbitol have been stable for 2-4 months. Several intense sweeteners and thickeners have been tested but are not compatible with the formulations. Taste masking compounds from flavor suppliers are compatible, but are designed to mask mild bitterness only. Sucralose, a new sweetener, and PVP and xanthan gum as a thickeners are being tested. A few lead formulations will be selected with analytical data generated.

## FLUOROFELBAMATE

Develop Fluorofelbamate for IND	High	Demonstration of Fluorofelbamate Safety Profile	Q2/FY03	HM/WH	Developing pre-clinical program only at this time "Go/No Go" for Phase I Study Fall/Winter.
Fluorofelbamate Drug Substance Synthesis	High	Drug Supply for Tox Studies and Development of Commercial Process	Q2/FY03	HM/WH	Synthesis of the 4th batch of crude fluorofelbamate has completed resulting total of ca. 4600 g of crude fluorofelbamate from four batches of operation. The material from four batches will be combined for final methanol/H2O crystallization after analytical data are obtained from each batch and confirm they are comparable to each other in impurity profile. CCMF, 39 g, and F-CCMF, 70 g, were from Magellan. These samples are designated for in vivo toxicity study.
Impurities required for Tox Studies	High	Drug Supply for Tox Studies	Q2/FY03	HM/WH	Magellan is developing a gradient elution HPLC method to monitor the fluorofelbamate manufacturing process. This method will provide a quick assay during various stages of reaction and purification of fluorofelbamate.

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## PRODUCT DEVELOPMENT(continued)

### FLUOROFELBAMATE (cont.)

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Analytical Methods Polymorph Screen	High		Q4/FY03	HM/WE	A polymorphs screen protocol was reviewed and approved. The study will start soon after the required PO is obtained.  HPLC analysis revealed two late eluting impurities in each batch of fluorofelbamate produced with the current process. The level of the two impurities is well above 0.1% in both crude and recrystallized material. LC/MS/MS study indicates that they could be the dimers of two fluoromonocarbamate connected through a carbonyl group. The exact structures of the two impurities may be elucidated by NMR and X-ray study of the isolated material or through synthesis.
Therimmune Pilot PK Studies	High		Q3/FY03	HM/BR/ WH	Sample of fluorofelbamate provided to Therimmune for pilot PK studies in rodent to determine saturation levels.

### GUAIFENESIN TANNATE

Product Design Discussions  Evaluate/Characterize Drug Substance	Medium	New Long Acting Form of Guaifenesin by JFC	On-going	ADD  EM/VP	ADD discussed modifications of GG Tannate with JFC chemist for drug product development. Initial characterization tests @ SSCI, were unable to define the nature of the Guaifenesin-tannate complex. Additional studies in progress for further characterization.
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### RYNA-12 TABLETS

Validate manufacturing process	High	New Tannate Tablet Product	Q2/FY03	VP	Validation report completed and approved. Acceptable results obtained for 3 month accelerated stability samples. Ryna-12 tablets released for commercial distribution on 8/28/02.
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## PRODUCT DEVELOPMENT (continued)

### SINUS-12 SUSPENSION AND TABLETS

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Sinus-12 Suspension	High	New Tannate Combination Products	Q3/FY03	GD/ML/ VP/CY	Sinus-12 Suspension samples for stability initiation received at Decatur on 8/15. Revised price quote signed 9/4/02. Testing of the suspension samples will take precedent over all method validation activities. Stability testing on laboratory prototypes will be performed for additional information.
Sinus-12 Tablets	High	New Tannate Combination Products	Q3/FY03	VP/GD /ML	Poor granulation flow characteristics observed with first full scale evaluation batch. Part of the batch will be used in stability study in an attempt to support launch. A second evaluation batch was manufactured in Decatur. Stability studies will be initiated ASAP.
Stability Programs	High			VP/GD/ML /CY	Review of capacity at Decatur to perform stability testing with additional resources. Price quotes approved 8/19 for first batch. Price quote approval required for second batch. Stability of first batch initiated on 8/16/02. Stability of second batch initiated on 8/26/02.
Assay Development and Validation	High			EM	EM submitted a detailed spreadsheet to Magellan to facilitate tracking of activities. Testing of the PE batch at Magellan has impacted completion of method validations in the time required.
Sinus-12 Suspension Potency Assay:				EM	Completion of potency method experiments targeted for 9/24, data reviewed by 10/8, and final report by 10/18. Investigations of the potency results (from the PE batch) which include using a 4 fold decrease in sample concentration and the use of alternative columns have been completed. The use of a step gradient to eliminate potential late eluting peaks is highly recommended. Accuracy testing completed for method validation have been received.

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## PRODUCT DEVELOPMENT (continued)

### SINUS-12 SUSPENSION AND TABLETS (cont.)

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Sinus-12 Suspension (cont.) Dissolution Assay:				EM	Completion of dissolution method experiments targeted 09/6/02, data reviewed by 9/13 and final report by 9/20. Results for specificity testing have been received. The use of a step gradient to eliminate potential late eluting peaks is highly recommended, and how the method has been validated.
Preservative Assay:				EM	Completion of preservative method experiments targeted 09/6/02, data reviewed by 9/20 and final report by 9/27. Results for accuracy testing have been received. The current method is sensitive to pH changes.
Sinus-12 Tablets Potency Assay:				EM	Completion of potency method experiments targeted for 9/20, data reviewed by 9/27, and report received by 10/4. Linearity, precision and solution stability have been completed.
Dissolution Assay:				EM	Completion of dissolution method experiments targeted for 09/20/02, reviewed 9/27, with report on 10/4. Results for specificity testing have been received, linearity, precision, solution stability, and filter validation have been completed.
Alternate Contract Laboratories				ADD/EM	Magellan is having difficulties in meeting timeline commitments. Alternate contract labs will be investigated. QTI has been contacted. Current CDA for MedPointe under review, will be updated if required.

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## PRODUCT DEVELOPMENT (continued)

SOMA Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Sustained Release Form. Labopharm	High		On-going	ADD/VP/ JH	Labopharm site visit conducted 8/29/02. Discussed product development strategies and reviewed experimental manufacturing facilities and testing laboratories.
Eurand					No further work will be performed at Eurand at this time.
Shire					Site visit to Additional Lab facility. Reviewed technology and capabilities.

### TUSSI-12 D SUSPENSION

Evaluate formulation without Sorbic acid	High		Q2/FY03	GD/VP/ML	Validation report completed. Acceptable results on 3 month accelerated stability samples from PE Lot D0206. PET testing on one qualification batch still required. Tussi-12D Suspension released from Decatur for commercial distribution on 8/29/02. EM obtained a price quote for the certification of Carbetapentane citrate as a primary reference standard at Magellan. Comparison to the Decatur SOP for standard certification in underway. Current procedure to determine standard potency at Decatur is a titration, both HPLC and titration shall be used to certify the standard.
Potency Assay:					
HPLC				EM	
GC			Q3/FY03	EM	Additional studies are required to address the accuracy failures during validation at the 70% and 80% levels. Upon completion of Sinus-12 suspension activities at Magellan additional testing will begin. Also additional extraction steps as recommended by VP will also be investigated.
Dissolution Assay:			Q3/FY03	EM	Method has been validated for the sorbic acid formula. Upon identification of improved chromatographic conditions as the current method has an unacceptably

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					short column lifetime, & poor chromatography the method will be revalidated.
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## PRODUCT DEVELOPMENT (continued)

### TUSSI-12 D SUSPENSION (cont.)

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Evaluate formulation without Sorbic Acid (cont.) Preservative Assay:			Q3/FY03	EM	Additional studies are required to address the specificity failures during validation. Activities at Magellan will begin shortly based on the chromatography developed for the SINUS-12 suspension.

### TUSSI-12D TABLETS

Formulation Development	High		Q3/FY03	GD/VP/ML	Launch Fall 02 Process evaluation batch scheduled for 8/14 – 8/16. The requisition for the batch has been initiated.
Stability Program	High		Q2-Q3 /FY03	VP/ML/CY WR	Price quote signed 9/4/02. Review of capacity at Decatur to perform stability testing with additional resources. Stability initiated on 8/26/02.
Validate/transfer analytical methods	High		Q3/FY03	EM/VP	EM submitted a detailed spreadsheet to Magellan so they may indicate all activities when completed, and reviewed by QA. Testing of the PE batch has impacted throughput at Magellan to complete the validations in the time required.
Potency Assay:				EM	Completion of potency method experiments targeted for 10/4, data reviewed by 10/18, and final report by 10/25.
				EM	Data from testing of developmental formulations made at Magellan indicate that a single HPLC assay can be used to quantitate all three actives. The use of an alternative column with increased lifetime (also to be used for the dissolution method) looks very promising, such that a single column and mobile phase conditions can be used for both dissolution and assay. Method conditions and development will be finalized by 9/6.
				EM	Completion of dissolution method experiments targeted for

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Dissolution Assay:					10/9, data reviewed by 10/18, and final report by 10/25. The use of an alternative column with increased lifetime and significantly improved chromatography looks very promising. Method conditions and development will be finalized by 9/6.
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# ADMINISTRATIVE

## PRODUCT & PROCESS DEVELOPMENT LABORATORY RELOCATION

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
OSHA Requirements	High	Safety of Laboratory Personnel	Q2	RM/EM	DOT awareness training price quote received, still waiting for confidential disclosure agreement from vendor.
Leasehold Improvements	High	Maximize Laboratory Functionality	Q2	ML/GB	Leasehold improvements are targeted for completion 7/22 and under budget. Fine tuning security system and physical systems. Installation of stability chamber monitoring interface is in progress. A burglar alarm system required for controlled drug storage has been installed but will not be activated until needed.
Central Files	Medium	Preserve Historical Drug Development Information	Q2	ML/CY	All files have either been archived or moved to the Cedar Brook facility. Consolidation and archiving will continue as time allows.
ATF License Controlled Drug License	Medium	Routine Lab Operations	Q2	ML	Renewal forms forwarded to F. Patterson for processing. Site and safe identified for drug storage.
Facility Contracts Set-up and manage contracts with vendors	Medium	Routine Lab Operations	Q2	ML/DW	Responsibilities assigned to facilitate set-up, billing, and management of various facility services accounts (utilities, vending, janitorial, laundry, etc.)
Facility Maintenance	Medium	Routine Lab Operations	On-going	ML/CY	Maintenance of electrical, plumbing, HVAC security and general operations. HVAC still not set/working properly. No quote received for HVAC contract. Roof leaks were reported after last heavy rainfall. Roofer is taking care of repairs. For safety reasons, a request for better lighting outside the building has been sent to Eastern Properties. The request has been forwarded to the building owner.

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