

**MedPointe Product & Process Development**  
**Program Priorities & Issues**  
**November 18, 2002**

## COMMERCIAL PRODUCT TECHNICAL SUPPORT



PTX0144-00001

### 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	JH/ADD/ CY	Task Force assembled to investigate path to implementation by Spring 03. Additional data from Regulatory submissions will be reviewed and summarized.
Qualify Marlex 5502BN Resin Stability program	High	Maintain Component Supply	Q3/FY03	CY/ML	Studies initiated to qualify transfer to new bottle resin. Additional samples (4.5 month) have been submitted for particulate testing. Results are expected by 11/22/02. The additional data is needed to perform a statistical analysis.
Valois VP3 Pump – Exclusive Supply Contract	Medium	Brand Protection		ADD	Discuss exclusive pump sales arrangement with Valois to limit potential use by future generics. Revised meeting date 11/15/02 at request of Sarah Malka of Valois.

### DORAL TABLETS

Qualify Decatur to manufacture Doral Tablets	High	Maintain Commercial Tablet Supply	Q4/FY03	VP/GD	Inter-departmental review of Marketed products resulted in recommendation to continue support of this project. Three timelines are available but there has been no commitment to any of these. Quotation requested from PMRS for development and manufacture of commercial supply. Request for compliance audit submitted.
Qualification of new drug substance supplier	Medium	Maintain Drug Substance Supply	Q3/FY04	HM/VP	Tateyama Kasei and FIS to be evaluated as suppliers of quazepam drug substance. Decatur has tested samples of quazepam from FIS. Samples passed USP testing, but were not micronized. FIS will provide pricing for micronization and activation of DMF. Cost of quazepam from TK for experimental work is available.

<sup>1</sup> BA-Beth Andry GB- Gul Balwani, ADD-Alex D'Addio, GD-Grace Dang, JG-Jeff Gazzara, WH-Weixuan He, JH-John Higson, ML-Mary Lehr, RM-Rick Majos, EM-Ed Mikalsen, HM-Hank Mortko, VP-Vithal Patel, WR-Will Robinson, BR-Bryan Roecklein, CY-Cindy Yayac

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- 1 -  
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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. The report containing three month stability data on first batch and second batch was approved on 10/28/02. Two lots of milled felbamate are currently under investigation: 2C0805 for particle size and 2E2007 for presence of foreign material.

### 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. A draft protocol has been received for comment.
Validate specificity for USP assay	High	Response to FDA Inspection	Q3/FY03	HM	Work initiated in response to FDA 483. Experiments for Depen and SOMA both completed. Final reports have been issued by Magellan.

### 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 – Mid Oct. 02. Magellan cannot achieve the salicylic acid retention time specified in the USP. Investigations are under way.
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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 – Mid Oct. 02. Magellan cannot achieve the salicylic acid retention time specified in the USP. Investigations are underway.
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- 2 -  
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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	Several formulations at higher active concentrations and/or higher viscosity have been stable physically at 4-6 month stability. Five formulations are selected for the second level of screening. Xemplar Pharmaceutical identified as alternate to Magellan for spray testing. CDA completed. Site visit on hold pending evaluation of financial stability of Xemplar.
Astelin Double-Strength – Proprietary pump design	Medium	Brand Protection		ADD	Valois has been contacted concerning the proprietary design of a pump for reformulated Astelin. Meeting re-scheduled for 11/15/02 at request of Sarah Malka of Valois.

## ASTELIN/STEROID COMBINATION PRODUCT

New Nasal Solution Product Azelastrine HCl and an Approved Steroid	Low	Extension Product for Lifecycle Maintenance	On Hold	ADD/VP/ GD/JH/JG	Project on hold based on evaluation of resources and analysis of success potential provided by R. Spivey.
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## 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	The preparation fluorofelbamate drug substance for preclinical toxicity study (ca. 4.2 kg) has been completed and the material has been tested and released to MedPointe. The Certificates of Analysis (COA) of all the batches of the fluorofelbamate have been reviewed and issued. Quotation approved for manufacture of GMP supply (2 Kg) of drug substance. Manufacture of GMP supply targeted for completion in January 2003. Validation of methyl carbamate method required for release.
cGMP Preparation of Fluorofelbamate	High	Phase I Clinical Study	Q2/FY03	HM/WH	F-diol, the penultimate of fluorofelbamate (ca. 2.2 kg) has been prepared in seven batches. All the material is in analytical division for certificate of analysis and material

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- 3 -

"MM/dd/yy" }

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					release when they are meeting the specification. Also, a composite sample is taken and a use test is planned soon.
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- 4 -  
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## PRODUCT DEVELOPMENT(continued)

### FLUOROFELBAMATE (cont.)

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Impurities required for Tox Studies	High	Drug Supply for Tox Studies	Q2/FY03	HM/WH	Bis-F-carbonate dimers isolated from fluorofelbamate drug substance and those derived from direct synthesis were compared by proton NMR and carbon NMR. Both experiments indicated that they are identical in structure. Currently, the study is focused on the preparation of 10-15g of the material to be used as a reference standard.
F-Diol Analysis	High			HM/WH	HPLC analytical method of F-diol has been developed which can successfully separate and quantify small amount of H-diol in F-diol. When the method is validated, it will be used in F-diol analysis and release before the cGMP campaign of fluorofelbamate.
Analytical Methods Polymorph Screen	High		Q4/FY03	HM/WH	Six different organic solvents and their different combinations have been screened and one major crystal form was identified except an unstable form (or a preferred orientation) was observed when the crystal was prepared by fast evaporation of method solvent. This result will be confirmed by repeating the experiment and calculating the XRPD powder pattern.  A single crystal of fluorofelbamate was generated in aqueous solution and crystallography data has been collected. The complete structure of the crystal form may be available soon.
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. Protocols for dosing solution development have been approved. PK plasma methods are being developed.
Phase 1 Clinical Trial and IND Submission				HM/WH/ML	A detailed timeline for Phase 1 clinical trial and IND submission is being developed. Meetings were held with Therimmune and IT to establish a procedure for electronic documentation exchange.

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- 5 -  
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## PRODUCT DEVELOPMENT (continued)

### GUAIFENESIN TANNATE

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Product Design Discussions	Low	New Long Acting Form of Guaifenesin by JFC	Ongoing	ADD	JFC has requested a commitment on GG Tannate development by their next board meeting on Dec 02. Recent communications by FDA indicate that successful development of guaifenesin tannate salt may require an NDA. C. Fishman and B. Pe to discuss with JFC this week.

### RYNA-12 TABLETS

Validate manufacturing process	High	New Tannate Tablet Product	Q2/FY03	VP	Three month data for the second & third qualification batches have not been received from Decatur. This data, as well as the six-month stability data (11/2) needs to be reviewed to ensure expiration dating is supported.
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### SINUS-12 SUSPENSION AND TABLETS

Sinus-12 Suspension	High	New Tannate Combination Products	Q2/FY04	GD/ML/ VP/CY	Process Evaluation - Sinus-12 Suspension data (D0208) look acceptable at 1 month. It is now at 3 month pull. PET testing at STS was supposed to start on 9/20/02 with only 5 USP organisms still has not been tested. Decatur is now testing it at Gibraltar.
Sinus-12 Tablets	High	New Tannate Combination Products	Q2/FY04	VP/GD /ML	Manufacturing of Sinus-12 tablet PQ batches delayed due to poor dissolution results for PE batch. Launch re-scheduled for August 03. The investigation of poor dissolution results for PE batches is underway. Dissolution-hardness profiles and other possible factors are being reviewed. The specification limits for tablet hardness and friability will be re-evaluated. Samples of the experimental batches manufactured at Magellan were received and testing is underway to compare the results of Magellan vs. MedPointe. Additional formulation experiments are on going to optimize the dissolution of the product.
Stability Programs	High			VP/GD/CY	Two month testing is in progress.

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- 6 -

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- 7 -  
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## PRODUCT DEVELOPMENT (continued)

### SINUS-12 SUSPENSION AND TABLETS (continued)

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
Sinus-12 Suspension Potency Assay:				EM	Validation report for assay method received, and is circulating for comments.
Dissolution Assay:				EM	Validation report for dissolution method received, and is circulating for comments.
Preservative Assay:				EM	Validation report for preservative method received, and is circulating for comments.
Sinus-12 Tablets Potency Assay:				EM	Validation report for assay method received, and is currently circulating for comments.
Dissolution Assay:					Validation report for dissolution method delayed as a number of method validation experiments were conducted without performing system suitability.
Alternate Contract Laboratories				ADD/EM	It is proposed that QTI assist in the method validation of the improvements committed to for the Tussi-12D suspension methods.
Transfer of methods to Decatur				EM/HM	Protocols have been signed and transferred to Decatur. Official method transfer testing still needs to be performed.

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- 8 -  
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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/GB	Data to support platform selection overdue. Status of method development unknown.
Shire					Site visit to Additional Lab facility. Reviewed technology and capabilities. Proposal reviewed and will be compared to an additional lab (Cardinal, Penwest).

### 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. Six-month stability data (11/2) needs to be reviewed to ensure expiration dating is supported. PET testing on one qualification batch (2H29) still has not started at STS. Decatur is testing it at Gibraltar. In addition, only the 5 USP organisms are available for testing at this time.
Potency Assay:			Q3/FY03		
HPLC				EM	A new method is needed that does not have Phenylephrine interference.
GC				EM	Additional studies are required to address the accuracy failures during validation at the 70% and 80% levels. A due date of Nov. 29 is targeted.
Dissolution Assay:			Q3/FY03	EM	Experiments underway, solubility using various mixtures of water 0.1N HCl, methanol, and acetonitrile completed.

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- 9 -  
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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	Studies are currently underway here to improve the Tussi-12 D suspension preservative method. The conditions from the Sinus-12 suspension are not suitable.

### TUSSI-12D TABLETS

Formulation Development	High		Q3/FY03	GD/VP/ML	Status of qualification batches to be discussed.
Stability Program	High		Q2-Q3 /FY03	VP/ML/CY WR	All two month data was received 11/13/02. Insufficient data for statistical evaluation of expiration dating. Disintegration results for tablets stored at 25C/amb RH in bulk and 20 ct package exceeded 30 minutes.
Validate/transfer analytical methods	High		Q3/FY03	FM/HM/ EM/VP	A protocol was developed to qualify Carbetapentane citrate analytical standard required for development due to limited supply at Decatur. Certification of Carbetapentane citrate (obtained from Sigma Chemical Co.) as a primary reference standard will be completed by 10/31.
Potency Assay:				EM	Validation report for assay issued on 10/9/02. Additional testing at the request of F. Martinez to demonstrate acceptable accuracy is obtained when adding solid tannate drug substances is underway at Magellan.
Dissolution Assay:				EM	Validation report for dissolution issued on 10/9/02. Plan for additional testing to determine the accuracy when adding solid tannate drug substance drafted and sent to Magellan (awaiting price quote).

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- 10 -  
"MM/dd/yy" }

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**TWINJECT**

Technical Support for Regulatory Submission By Hollister-Stier	High		Q3/FY03	HM	Monarch Laboratories site visit by HM 9/27/02 to review extractables method validation. Provided data analysis on stability data to HS.
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**ADMINISTRATIVE****PRODUCT & PROCESS DEVELOPMENT LABORATORY RELOCATION**

<b>Issue/Program</b>	<b>Priority</b>	<b>Critical Path</b>	<b>Timing</b>	<b>Manager</b>	<b>Status/Comments</b>
OSHA Requirements	High	Safety of Laboratory Personnel	Q2	RM/EM	DOT awareness training conducted on 11/04/02.  A Liquid/Solvent waste log was drafted and sent out for comments.  The emergency lighting was tested. One emergency light in lab 133 was not functional.
Leasehold Improvements	High	Maximize Laboratory Functionality	Q2	ML	Roof repairs to properly seal a roof penetration need to be made.
Central Files	Medium	Preserve Historical Drug Development Information	Q2	ML	Filing and archiving of files is ongoing.
ATF License Controlled Drug License	Medium	Routine Lab Operations	Q2	ML	The application for our DEA license has been received. Barbara Beckley will complete and file the application.
Facility Contracts Set-up and manage contracts with vendors	Medium	Routine Lab Operations	Q2	ML/CY	Facility contact vendor maintenance is consuming a substantial amount of personnel resources. Various solutions to this problem are being examined.
Facility Maintenance	Medium	Routine Lab Operations	On-going	ML/CY	Maintenance of electrical, plumbing, HVAC security & general operations. Alternate contractor being investigated.
Budget Preparation	High	Fiscal 2003/2004	Q3	ML	A budget package was distributed to department heads. First draft targeted for completion by 11/15/02.

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- 11 -  
"MM/dd/yy" }

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## ADMINISTRATIVE (continued)

### PRODUCT & PROCESS DEVELOPMENT LABORATORY RELOCATION

Issue/Program	Priority	Critical Path	Timing	Manager	Status/Comments
GMP/GLP Laboratory				ML/HM/ ADD	Management has directed us to develop a timeline for bringing the laboratory into GLP/GMP compliance. Meetings were held on 9/20 and 9/27 to discuss issues. Several action items were identified to initiate the process of bringing the laboratory into GLP/GMP compliance. A template CV was distributed for completion and inclusion in the personnel files. Position descriptions are also needed for the files.
				EM	The dissolution equipment calibration completed.
				EM/BA	A significant amount of time has been spent installing two (2) 1050 HPLCs, and performing the maintenance required so they are operating properly, i.e., pump heads, check valves, and active inlet valves. Parts, and communication cables, have been pooled between the four (4) instruments we have to get two operational.  A justification memo was written for \$62,000 for complete IQ,OQ,PV of four 1050 HPLC units. Approval is needed so the equipment can be used for analytical development activities here.

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- 12 -  
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