Section18:Protection of the Finished Product

The entire facility has been designed to meet or exceed US cGMP manufacturing guidelines. A US engineering company (VECO-Rapley) with extensive experience in design of multi-purpose batch API facilities was employed to provide concept and detailed design throughout. Additionally, "subject-matter" experts, with direct API experience in the US pharmaceutical industry have been utilized in design review and specification as owner's representatives. They will remain with the project through plant start-up and validation to ensure adequate training of on-site personnel and the appropriate transfer of API cGMP technology. Fields represented are Quality Assurance, Quality Control, Maintenance, EH&S, Process Engineering, Process Automation, Materials, Finance, as well as Operations and Kilo Lab management.

Conceptual Design Principles

The fundamental design philosophy followed has been to physically separate all solids handling areas (including raw material charging) from other plant areas and to provide separate air handling systems for each of the seven production suites. Therefore, within the plant, there will be no exposure of product to possible contaminants. Protection levels were defined for all plant areas in accordance with the 1996 ISPE/FDA Baseline Pharmaceutical Engineering Guide Volume 1, Bulk Pharmaceuticals. All engineering and construction has proceeded following the HVAC design and architectural finishes specified in our "Basis of Design" document This design was then reviewed with the US FDA in May of 1997 in a formal Pre-Construction Review meeting. Following this meeting, they stated that if we implement the design submitted, we would have a state-of-the-art API facility. They also indicated that our presentation of the design principles and basis was among the best that they had seen.

Specific Protection by Area

Throughout the facility production will occur in nine segregated manufacturing suites that are temporarily devoted to a single product. Corridors separate each suite from the others. Air pressure within each suite is maintained negative with respect to the corridors, with pressure differentials continuously monitored. Final protection for final product handling is accomplished by two different methods:

* Kilo Lab and Mini Plant: These facilities are constructed to meet all criteria for handling high potency compounds. All solids, including final filtration and drying, are contained in glove boxes. Containers using alpha/beta connections are used for any solid transfers.

* Pilot Plant, Small Manufacturing Unit, and the three Production Bays: Each of these is provided with its own separate "Finishing Train". Each train consists of a Crystallizer, Heinkel centrifuge, Krauss Maffei dryer and final product hopper and packaging. This is a totally closed system, purged with filtered nitrogen, arranged vertically to allow for short gravity feeds of

material from one piece of equipment to the other, and with each major piece in its own closed room. Milling requires a second trip through the packaging unit using closed containers for material transfer. Final packaging occurs utilizing the continuous liner method, in the highest protection area, level 3a controlled. This includes 95% filtration of supply air, 100% fresh air, suitable airlocks, continuous pressure differential monitoring, and environmental monitoring for viable/non-viable particulates. Each drying train has its own separate HVAC and vacuum systems.