

**TYPICAL CONSULTING SERVICES PROVIDED BY
AVETA LIFESCIENCES PVT. LTD.**

May, 2007

1.0 INTRODUCTION

Aveta Lifesciences Pvt. Ltd. was founded to provide process, technical, GMP & regulatory guidance to the Indian BioPharma marketplace. Aveta's mission is to bring lean, compliant quality & manufacturing systems to the suppliers of ethical drug products to ensure safe drugs to people throughout the world.

2.0 COMPANY BACKGROUND

Aveta Lifesciences (Aveta) is a strategic partner with Pharmatech Associates, Inc. (USA) (Pharmatech) to answer a worldwide need to develop best practices and an environment of quality throughout the bio/pharmaceutical industry. Through our affiliation we provide over 12 years of proven experience in helping our clients to achieve a better return on their investment by driving quality deep in to the process of the discovery, development, operations, manufacturing and supply chain groups. Aveta Lifesciences is a methodology driven company. We approach all solutions from both the inherent process that underlies any operation and a lens of FDA / EU compliance so that each solution has the leanest precursors of success to the product and the business. Aveta & Pharmatech have positioned themselves to be thought leaders in the bio/pharmaceutical industry in process, quality & compliance. In this regard we have several process patents pending, are invited to speak at conferences around the world and have published white papers on many of the emergent problems in our industry. Aveta retains industry

professionals with proven experience in the development and deployment of all facets of the drug development lifecycle, focusing on providing guidance and solutions which are both compliant with today's risk based regulatory requirements and can be implemented given the capabilities of each client's organization. This breadth of knowledge and understanding of the drug development process allows Aveta to integrate technical, quality system and regulatory guidance into all activities to provide the best practice solution with the least amount of cost.

2.1 **Proven Methodology**

Aveta & Pharmatech have significant experience in commissioning, qualification and validation of medical device, solid dosage, parenteral and biopharmaceutical operations. Experience, however, by itself is not always sufficient to ensure a project's success. In order to be successful and navigate the complexities of organizational, regulatory, technical and quality system dynamics, Aveta & Pharmatech have developed a methodology that is proven and provides a framework to ensure the success of a project.

The methodology consists of three essential elements for project success: Relationship management; clear program requirements; and project structure. Supporting these three elements are processes & procedures that comprise Aveta's toolkit for success.

2.1.1 **Relationship management** refers to developing a strong relationship with the key stakeholders of the program. This could be the General Contractor for new construction programs, equipment suppliers, validation, QA, QC,

facilities, engineering and/or project management. By ensuring all interested parties are apprised of the program's plans and progress, there is very little possibility for misunderstanding. This communication can be managed through a single client contact individual such as the Project or Construction Manager (Section 3.4) or through a series of regular project meetings. Regardless of the vehicle, Aveta's Project Manager will ensure all critical issues pertaining to the project are considered as the program proceeds.

2.1.2 **Clear program requirements** refer to ensuring all members of the team are clear regarding what the objective of the scope of work is. In many cases, client developed User Requirement Specifications (URS) or consulting scopes of work are not fully developed which reflects the often evolutionary nature of design / development process for equipment, procedures and/or specifications. Aveta will ensure all critical elements are agreed to before proceeding with an activity that could cost the project time and money. Understanding the client's quality strategy is also a critical element in ensuring all activities will meet the business need.

2.1.3 **Project Structure** refers to ensuring that there is a clear organization in place for handling decisions in the execution of the project. In some circumstances, the specific requirements for a design / characterization /

optimization of a process(es) cannot be clearly defined until initial investigations have been conducted and a specific scope can be reached. Having a process in place to ensure that all key stakeholders are satisfied and have buy-in with the approach to the project prior to and during execution will reduce concerns about both budget and schedule. In those cases where complex processes are being deconstructed and analyzed for characterization it is helpful to have a single team member acting as a conduit for information and the dissemination of design of experiments (DOEs) for process improvements. This communication can greatly improve the efficiency of the review and approval process toward a full characterization and thus a fully defined scope of work.

2.2 Experience

Consulting: Aveta has the depth of expertise to cover virtually all aspects of the Regulated Life Science industry. With Aveta & Pharmatech's many years of technical industry experience, we have both a deep understating of the needs of our customers' development and/or GMP regulatory requirements and the operational considerations that impact the bottom line. As well, our Compliance Consultants combined, have over a hundred years of hands-on FDA investigational experience that make Aveta's offering to the Bio/Pharmaceutical marketplace unique; we

approach every solution within the context of a technical, operational and compliance perspective. A sampling of our consulting offerings can be found in Section 3.

Training: Like our Consulting Group, Aveta has qualified experts in almost every field within the Regulated Life Science industry. Our professionals are well versed at both the hands-on execution of the work and the dissemination of that work to others. Many of our experts have written books or have been involved with the development of courses or have written technical papers for equipment handling & maintenance, operational excellence, GMP integration, compliance, standards, validation or a wide range of other topics. Aveta approaches training as we do all solutions, from a process and methodology point of view. We train not only to the task but also to the context so that our trainees are fully able to perform not only their work, but understand their role within the greater operational environment so as not to negatively impact surrounding operations. A sampling of our training offerings can be found in Section 3.

3.0 TYPICAL SERVICES

Following are a listing of typical services offered by Aveta Lifesciences:

- 3.1 **Regulatory & process gap assessment:** RLL is requesting assistance from PAI to perform a cGMP audit / gap assessment of one of their solid dosage production facilities in India. PAI is recommending that

the project be divided into two phases: The first phase addressing the compliance aspect and gap analysis against FDA API Pre-Approval Inspection criteria as defined by ICH Q7A and FDA Compliance Program 7356.002F, API Process Inspections; and the second phase creating a customized specific remediation focused on the gaps identified in the audit. The scope is as follows

- 3.1.1 Phase 1: The gap assessment will include the following systems / areas of inspection:
 - 3.1.1.1 Quality Systems: Quality Policy; Document Control; Process Change Control; Training; Investigations (including OOS) / Deviations; Corrective Actions/Preventive Actions (CAPA); Customer Complaints; Product Disposition; Internal Audit Program; Vendor Audits (Handled by RLL); Electronic Systems; Multi-use Policy; Master Validation Plan & Associated Procedures; Calibration Program; Standard Operating Procedures (SOPs); and disaster recovery;
 - 3.1.1.2 Regulatory Compliance: Policies and procedures related to regulatory filings (DMF, IND, NDA, ANDA, etc.), updates and annual reports. The gap assessment will include the review of one ANDA or NDA filing for one product.
 - 3.1.1.3 Production Systems: Warehousing and Inventory Control; Material Receiving; Production Records and Controls; In-process Controls; Water System(s); Environmental Monitoring; Housekeeping, Pest Control, & Security; Lot Numbering & Lot Controls; Reprocessing & Rework; Final Product Storage, Distribution and Control; Material Handling & Controls; Buildings & Facilities Equipment; waste stream management; and Preventive Maintenance Program(s);
 - 3.1.1.4 Quality Control Labs: QC Lab; Instrumentation; Laboratory

Analysts; Stability Program; Out of Specification Results (OOS); Retain Samples; Sample Handling

3.1.1.5 Qualification / Validation:

3.1.1.5.1 Operations: Review of the Master Validation Plan for the facility & manufacturing

3.1.1.5.2 Facility: GMP Utility Systems & Equipment; HVAC & Environmental Monitoring; Facility GMP Release for Production

3.1.1.5.3 QC Laboratory: GLP Laboratory Equipment; Methods Process Validation

3.1.1.5.4 Production: Manufacturing Equipment; Computer & Part 11; Automation Systems; Cleaning Validation

3.1.1.5.5 Product: Process Validation

3.1.1.6 Preliminary report to auditing staff & key stakeholders: A verbal / PowerPoint initial review of gaps found during investigation, to be divided into Critical / Major & Minor with some verbal discussion around potential gap closure for the Critical & Major items.

3.1.1.7 Final Report on Gap Analysis: Full system by system report on identified gaps in the quality system environment with suggested options for remediation of Critical & Major gaps.

3.1.2 Phase 2: Implementation plan for gap closure based on gaps identified in the audit. The scope and pricing for this phase to be determined after gap analysis of quality systems.

3.2 **Facility Qualification & Continuous Monitoring:**

3.2.1 Facility Qualification: An in-depth investigation & analysis of the existing documentation to support the qualification of a multi-product solid dosage manufacturing facility. Scope to include:

3.2.1.1 The leveraging of the compliance & process gap analysis (item #3.1 above) for the following: Multi-use Policy; Facility: Master Validation Plan; GMP Utility Systems & Equipment; HVAC IOQ; Facility GMP Release for Production

3.2.1.2 Additional in-depth review of Basis of Design (BOD) inclusive of the following:

3.2.1.2.1 Building Operational Flows

3.2.1.2.2 Critical facility utility systems review of as-built construction and P&IDs drawings inclusive of any:

- Clean utilities and power distribution for capacity, redundancy & back-up
 - 3.2.1.2.3 HVAC system review of as-built construction and P&IDs drawings inclusive of: HVAC AHU's; duct distribution; and pressure cascade
 - 3.2.1.3 Provide an implementation plan for remediating any deficiencies inclusive of hands-on assistance in the reworking of SOPs, training on the new SOPs and developing metrics for both the facility & personnel to measure success going forward.
- 3.2.2 Continuous monitoring of facility (Environmental Monitoring):
Scope to include:
 - 3.2.2.1 The leveraging of the compliance & process gap analysis (item #3.1 above) for the following: Master Validation Plan; Calibration Program; SOPs related to EM; Out of Specification Results (OOS); and Sample Handling
 - 3.2.2.2 Additional in-depth review of HVAC PQ Validation reports; HVAC PQ mapping; continuous monitoring mapping; QC assays associated with EM; and sample & personnel flows associated with EM and potential contamination or cross contamination issues.
 - 3.2.2.3 Provide an implementation plan for remediating any deficiencies inclusive of hands-on assistance in the reworking of SOPs, training on the new SOPs and developing metrics for both the facility & personnel to measure success going forward.
- 3.3 **Quality Systems:** An in-depth investigation & analysis of the existing documentation to support the qualification of a multi-product solid dosage manufacturing facility. Scope to include:
 - 3.3.1 The leveraging of the compliance & process gap analysis (item #3.1 above) for the following: Quality Systems: Quality Policy; Document Control; Process Change Control; Training; Investigations (including OOS) / Deviations; Corrective Actions/Preventive Actions (CAPA); Customer Complaints; Product Disposition; Internal Audit Program; Vendor Audits (Handled by RLL); Electronic Systems; Multi-use Policy; Validation Policy and Program; Master Validation Plan & Associated Procedures; Calibration Program; Standard Operating Procedures (SOPs); and

disaster recovery.

3.3.2 Additional in–depth review of the following:

3.3.2.1 Specific system by system analysis of security, protection, process flows for compliance for each of the following systems or processes:

3.3.2.1.1 Documentation

3.3.2.1.2 Training

3.3.2.1.3 Deviation / CAPA Management (incl. OOS & OOT)

3.3.2.1.4 Log book maintenance

3.3.2.1.5 Internal & Vendor Audit process

3.3.2.1.6 Calibration, Preventive Maintenance & Validation

3.3.2.1.7 Raw Material & API Qualification & Release Process

3.3.2.1.8 Lot Release Process

3.3.2.1.9 ERP to MES to SCADA to Machine Computer Validation

3.3.2.1.10 Product & Methods Validation Process

3.3.3 Provide an implementation plan for remediating any deficiencies inclusive of hands–on assistance in the reworking of systems, process flows, SOPs, training on the new SOPs and developing metrics for both the facility & personnel to measure success going forward.

3.4 **Training & Guidance:** Aveta’s experts are able to provide training in the following areas:

3.4.1 Quality / Compliance Training & Guidance:

3.4.1.1 Aveta and Pharmatech have former FDA compliance personnel on staff that have decades of experience both within the FDA and within industry. Their approach to compliance is based on applying the appropriate level of oversight & guidance to the product and/or process involved related to the phase of product development from early phase development through ANDA or NDA licensure..

3.4.1.2 Policy level training in GMPs, FDA approach to sustained compliance, FDA / EU approach to pharma–business ethics, multi–use facility boundaries and building Quality into operations to reduce overall cost and time to market.

3.4.1.3 Documentation: FDA & ICH requirements regarding GMP documentation skills for the development, writing, reviewing, editing, approving, and retiring of documents

- 3.4.1.4 Change Control: FDA & ICH compliant flows that clearly define the boundaries around which change controls are required. Because of Aveta's strong Six Sigma & Lean Manufacturing background, our experts approach the change control environment from an extremely lean lens of compliance that avoids much of the confusion that can be generated in initiating & closing complicated change controls. Aveta imparts this approach in a systematic way to [seems to be missing text]
- 3.4.1.5 Deviation / Corrective and Preventative Actions (CAPA) System: FDA & ICH requirement implementation through a lens of Lean & Six Sigma KPI's to provide a systematic context in which to evaluate types and severity of deviations and whether they need to become CAPAs.
- 3.4.1.6 Computer systems: FDA, ICH & Lean targeted training to the IT Quality Manager to clearly define the role of IT within a regulated manufacturing & operational environment. Follow-on training to the IT group at large to define the role and boundaries of computer techs in the Quality environment.
- 3.4.1.7 Audit / Inspection Prep: Lean approach to preparing, holding & responding to FDA & EU audits and / or inspections.
- 3.4.1.8 Lot Release: A lean cross-functional process approach to product lot release to decrease errors, increase efficiency and reduce time to release lots to market targeting US & EU requirements.
- 3.4.1.9 Process Development, Tech Transfer, Manufacturing, Lean, Six
- 3.4.2 Six Sigma, Etc: Aveta is capable of hands-on training / guidance / teaching on any of the following subjects and / or processes:
 - 3.4.2.1 Process & Development:
 - 3.4.2.1.1 Process Development
 - 3.4.2.1.2 Process / Product Characterization
 - 3.4.2.1.3 Pharma & Biotech Process / Product Development
 - 3.4.2.1.4 CMC Development & Management (PQAS)
 - 3.4.2.1.5 Risk Management in Product Development
 - 3.4.2.1.6 Quality by Design (ICHQ8)

- 3.4.2.1.7 Applying ICH Q9/10
- 3.4.2.1.8 Equipment
 - Design/Installation/Operation/Maintenance
- 3.4.2.1.9 Tech Transfer
- 3.4.2.1.10 Process Validation: Design Space
- 3.4.2.1.11 Process flows
- 3.4.2.1.12 Value Stream Mapping
- 3.4.2.1.13 Aseptic Processing for Parenterals, Ophthalmic, Injectables, Vaccines, etc.
- 3.4.2.1.14 Process Analytical Technology (PAT)
- 3.4.2.1.15 Lean/Six Sigma for the BioPharma Industry
- 3.4.2.1.16 Biopharmaceuticals, proteins and APIs
- 3.4.2.1.17 Gene and Cellular Therapies
- 3.4.2.1.18 Oral Solids for Immediate, Modified and Sustained Dosage Forms, Dry Powder Aerosols
- 3.4.2.1.19 Semi Solids that includes Ointments, Creams (emulsions and suspension), Gels, Suppositories and Transdermals
- 3.4.2.1.20 Liquid Dosage Forms (syrups & elixirs)
- 3.4.2.1.21 Drug Delivery, Drug Eluting Stents and novel delivery systems
- 3.4.2.2 Analytical & Problem Solving:
 - 3.4.2.2.1 Kepner–Tregoe
 - 3.4.2.2.2 Quality by Design
 - 3.4.2.2.3 Lean/Six Sigma for the BioPharma Industry
 - 3.4.2.2.4 Root cause analysis & remediation
 - 3.4.2.2.5 Process Analysis & Targeted Improvement
 - 3.4.2.2.6 Analytical Method Development (ICHQ2a)
 - 3.4.2.2.7 Analytical Methods Validation
 - 3.4.2.2.8 Sample Design & Management
- 3.4.2.3 Quality, Operations & Validation:
 - 3.4.2.3.1 Risk–based GMPs & cGMPs (21CFR 210 and 211)
 - 3.4.2.3.2 API GMPs (ICHQ7)
 - 3.4.2.3.3 Quality by Design (ICHQ8)
 - 3.4.2.3.4 Supply Chain Development/Analysis/Risk Mitigation
 - 3.4.2.3.5 Facility design & construction
 - 3.4.2.3.6 Validation Strategy/Master Plan/Assessment

- 3.4.2.3.7 Facility/Utility Qualification
- 3.4.2.3.8 Equipment Qualification: Design & Operations
- 3.4.2.3.9 Cleaning Validation: Solubility & Toxicity
- 3.4.2.3.10 Packaging Validation: Primary & Secondary
- 3.4.2.3.11 CAPA system development and deployment
- 3.4.2.3.12 Document system development and deployment
- 3.4.2.3.13 Training system development and deployment
- 3.4.2.3.14 Preventive Maintenance system development and deployment
- 3.4.2.3.15 Calibration system development and deployment
- 3.4.2.3.16 Risk Based Validation
- 3.4.2.3.17 Risk Management (ICHQ9/10)
- 3.4.2.4 Compliance
 - 3.4.2.4.1 International Organization for Standardization (ISO) systems & documentation
 - 3.4.2.4.2 FDA Guidelines
 - 3.4.2.4.3 ICH / EU Guidelines
 - 3.4.2.4.4 Drug Master File (DMF) filing
 - 3.4.2.4.5 IND / NDA / ANDA filing
 - 3.4.2.4.6 Compliance Requirements for Canada, Japan, S.A., UK, etc.
 - 3.4.2.4.7 Sponsors / Monitors, Institutional Review Board
 - 3.4.2.4.8 Compliance Assessment on Clinical Investigators
 - 3.4.2.4.9 Phase I–IV Clinical Trial Assessments
 - 3.4.2.4.10 483 / Warning Letter / Consent Decree Remediation Guidance
 - 3.4.2.4.11 PQAS Strategy
 - 3.4.2.4.12 Risk Based Inspection Readiness
 - 3.4.2.4.13 Compliance Leadership Responsibility in the US & EU markets
 - 3.4.2.4.14 Mock Bioresearch Monitoring Program (BIMO) Inspections
 - 3.4.2.4.15 USP National Advisory Committee
 - 3.4.2.4.16 Potential Drug Association Guidance Review Committee
- 3.4.2.5 Automation & Computer Systems
 - 3.4.2.5.1 Scale up for automation and/or large scale commercial production and licensing

- 3.4.2.5.2 GAMP4
- 3.4.2.5.3 Part 11 Compliance
- 3.4.2.5.4 Electronic Batch Records
- 3.4.2.5.5 Electronic Signatures
- 3.4.2.5.6 Computer Validation
- 3.4.2.5.7 IT Infrastructure Inspection Readiness

3.5 **Project Management and Project Controls:**

- 3.5.1 Aveta can provide project management in the following areas:
 - 3.5.1.1 CMC Leadership: Role is to manage the Chemistry / Manufacturing / Control team; bring together process characterization, quality control, process development (scale-up and/or optimization), manufacturing & quality to develop and publish documentation for regulatory filing(s); in conjunction with the GMP Integration Project Manager is responsible for the technical side of the development of the process validation protocols.
 - 3.5.1.2 Product Management: Role is to coordinate the regulatory, quality, process development, production/manufacturing & business strategy to meet the overall requirements to license product(s).
 - 3.5.1.3 Project Construction Manager: Role is defined as the owner's representative to the engineering & construction team from early design documents through to final commissioning. Work includes: Vendor selection; ROM budget estimates; ROM high level scheduling; specification & submittal review; drawing review for constructability and adherence to the BOD & URS's; coordination between contractor's schedule and client schedule; reviews & recommends for approval contractor's quantities for payment; coordinates activities between construction contractors, operations group, quality group, and outside vendors / parties. This person is the conduit for all information related to the facility construction & equipment installation.
 - 3.5.1.4 Project Director for Plant Design through Construction through GMP Implementation and Process Validation. This role begins at the initial design concept phase of a project to ensure that the plant is designed from the manufacturing

process out using QbD and Lean Manufacturing principals within the context of FDA/EU compliance standards. This allows for the fastest track with the least amount of waste with respect to power, water, clean utilities, operational flows and product risk. The PD leads the development of the BOD, the Utility URS's, any required modification to existing Quality Policies and works with client management in Design & Construction vendor Qualification & Selection. Over the life of the project the PD oversees multiple PM's and client team leaders to coordinate each phase of work to track, enable and, if needed, push teams to keep to their milestones for successful project delivery. The PD works closely with the Project Controls lead to track the KPI's of the project so that the client's management team is aware of any impending difficulties months in advance of the occurrence of the problem so that the team(s) can proactively remove or work around obstacles long before they impact the project.

- 3.5.1.5 Project Director for Compliance Remediation related to FDA Warning Letters or Consent Decree Remediation. This role acts as an outside 3rd party management representative to push internal departmental teams to correct audit findings and acts as the coordinator & mediator in resolving cross-functional gap closures. The PD also assists the regulatory group in their interactions with the Regulatory Agencies to provide accurate information regarding the status of the remediation.
- 3.5.1.6 Automation Project Management for URS development, Risk Analysis (AFMEA), Design, Trace Matrix maintenance, FRS review, DDS/SDS/IDS Reviews, Design Review, FAT/SAT development & execution, installation oversight, Preventive Maintenance SOP development and operational implementation.
- 3.5.1.7 Validation Project Manager: Responsible for the overall scope of facility, equipment and cleaning validation as well as the execution of the process validation (process validation protocol development is handled between the Product Manager or CMC Manager and the GMP Integration

Manager). Role can include assisting in the development of the Validation Master Plan through a lens of “Risk Based Validation” and does include the development, coordination and oversight for all validation protocols and routings for approval; prior to execution, the VPM ensures that the commissioning & TOP documentation aligns with the validation protocols; during execution of the protocols, the VPM oversees and provides execution approval for all validation reports and coordinates internal approvals by client team members.

3.5.1.8 GMP Integration Project Management: Lead employee teams in the development of best practice operational SOPs that focus on driving quality in to the process; role can take over from construction at the end of commissioning and the beginning of validation to ensure that the construction contractors provide appropriate TOP documentation to accelerate the validation process; acts as operations liaison during validation to ensure best sequencing for manufacturing coming on line; takes the entire GMP operations group through the process of integrating the GMP SOPs into daily operations by coordinating internal departments for SOP writing, training & start up of manufacturing; assists in sequencing all start-up activities to Area Release (including HVAC PQ & shake down runs) and the eventual qualification & process validation lots. This role, in conjunction with the CMC Manager is responsible for the operational side of the development of the process validation protocols. This role can also be leveraged as a catalyst for departmental development when transitioning from a development or Phase II company to a GMP commercial operations one.

3.5.2 Project Controls: Aveta’s team can provide either stand alone services to augment the client’s management/technical/construction team or can act as an integrated element with Aveta’s project management team to provide a seamless delivery of a project at any interval along the drug development lifecycle. Aveta Project Controls offerings:

3.5.2.1 Planning from initial concept through to market launch

- 3.5.2.2 Scheduling at all parts of the drug development life cycle including both internal deliverables (SOPs, protocols, recipes, lot release, etc.) or external deliverables (design, construction, equipment lifecycle, validation, regulatory audits, etc.)
- 3.5.2.3 Cost Control Management for all parts of the project lifecycle
- 3.5.2.4 Cost of Goods (COG) analysis
- 3.5.2.5 Production Forecasting & Planning
- 3.5.2.6 Preventive Maintenance & Calibration Planning
- 3.5.2.7 Resource planning, modeling & management for both internal & external requirements.
- 3.5.2.8 Project Controls system development. Aveta's team can provide consulting services to assist clients to select the appropriate Project Controls solution for the size / mix of the company. Our PC team assists with the evaluation of the clients specific needs, software selection, software implementation, operations implementation including SOP development and employee training. This approach allows the client to walk away with the full capability to do Project Controls going forward. If this is selected as an option prior to the start of a significant capital project where these project controls will be used to manage the project, then much of the implementation phase becomes integrated with the project thus saving time & cost as well as providing a perfect training ground for internal project controls resources going forward.

3.6 **Equipment & Automation Expertise:** Aveta has a team of experts provide process excellence on multiple levels. With many years of experience in a technical development, manufacturing operations, automation design, computer validation, PAT development, eBR implementation Aveta's team has the depth of knowledge to assist clients in developing fully GMP & operationally integrated automation solutions. Following is a representative list of the expertise that Aveta offers in equipment & automation:

- 3.6.1 Equipment Lifecycle
 - 3.6.1.1 Process Evaluation & Risk Analysis
 - 3.6.1.2 URS/FRS Development

- 3.6.1.3 Vendor Qualification & Selection
- 3.6.1.4 Software & Validation
- 3.6.1.5 Electronic Batch Record Development & Implementation
- 3.6.1.6 Equipment Design
- 3.6.1.7 Process Analytical Development, Analysis & Deployment
- 3.6.1.8 Automation Project Management
- 3.6.1.9 TOP Development
- 3.6.1.10 FAT & SAT Development & Execution
- 3.6.1.11 Operational & Preventive Maintenance SOP Development
- 3.6.1.12 Validation strategy, implementation & execution:
 - 3.6.1.12.1 Facility Validation
 - 3.6.1.12.2 Equipment Validation
 - 3.6.1.12.3 Automation Validation
 - 3.6.1.12.4 Cleaning Validation
 - 3.6.1.12.5 Process Validation
 - 3.6.1.12.6 Environmental Monitoring
- 3.6.1.13 “Go live” operations
- 3.6.1.14 Continuous Compliance through monitoring & metrics
- 3.6.1.15 Deviation / CAPA, Process Optimization & Change Control
- 3.6.1.16 Decommissioning & Decontamination
- 3.6.2 Aveta has expertise regarding all equipment & utility systems that relate to Biotech, Pharmaceuticals, GLP Labs, GTP Labs & Manufacturing. As well, Aveta along with Pharmatech are world thought leaders in Process Analytical Technology development & implementation. Our holistic approach to equipment includes the design, installation, validation, operation, cleaning & contamination issues, preventive maintenance and continuous compliance. Following is a representative list of equipment that Aveta has hands-on experience with:
 - 3.6.2.1 Solid dosage, capsule, liquid & cream manufacturing: Granulators; blenders; tablet presses; pan coaters; fluid bed coaters; GPCG & Wurster columns; tablet printers; encapsulators; soft gelatin technologies; sterile filling; packaging; tablet counting; labeling; homogenizers; etc.
 - 3.6.2.2 Biotech manufacturing: Cryogenic storage & management; inoculation & incubator equipment; bioreactors; bag reactors; jacketed tanks; harvest vessels & centrifugation; UF/DF skids; purification columns; formulation tanks &

carboys; freeze/thaw storage vessels; lyophilization equipment; filling equipment for vials & syringes.

- 3.6.2.3 Utilities: Clean power, back-up generation & UPS equipment; water treatment; RODI water plants; WFI plants & storage equipment; CIP 100, CIP 200 & SIP systems; parts washers and autoclaves; HVAC equipment; BMS to maintain pressure cascades, temperature, humidity and particle counts; steam plant & clean steam generation; CDA & CCA generation; N₂, O₂ and other bulk gas distribution systems inclusive of supply chain / cold chain & quality release issues.
- 3.6.2.4 Supply Chain / Cold Chain: Warehouse design & constructability issues; high pile storage racking considerations; automated warehousing; refrigeration & freezer equipment; production planning, pedigree & work flows associated with GMP raw materials, components and API; transportation considerations & validation; RFID & other traceability / security devices.
- 3.6.2.5 QC Laboratory: Approach to all equipment from a GLP reference. Typical equipment might include: BioSafety Cabinets; microscopes; electron microscopes; HPLC's; PCR equipment; sample storage equipment; LIMS; cell counters; scales; etc.
- 3.6.2.6 Medical Devices & Combination Products: As this item varies from product to product, Aveta's approach to these devices is to start at the analytical and / or mechanical limits of failure, perform Design for Six Sigma (DFSS) analysis of the process and evaluate if the equipment selected meets the limits of the process for the product. With combination products, Aveta & Pharmatech have many years of experience at assisting medical device companies to incorporate the more rigorous standards for GMP products and for GMP manufacturing companies to understand the nuances of novel or complex delivery systems and how best to strategize a comparability program.

- 3.7 **Process Risk Assessment:** Aveta, as a Lean & Six Sigma process driven company, has many years of proven success at problem solving from a

risk based approach. Following are some examples of regulatory, analytical & quality approaches utilized by Phamatech's team of experts:

- 3.7.1 cGMP for the 21st Century: Risk Management (2002)
- 3.7.2 Process Analytical Technology: Process Control through better science (2003)
- 3.7.3 The Critical Path: To encourage innovation (2004)
- 3.7.4 The Future Desired State: White paper (2004)
- 3.7.5 HACCP – Hazard Analysis and Critical Control Points
- 3.7.6 Fault Tree Analysis – Top Down Approach
- 3.7.7 FMEA – Failure Mode and Effects Analysis
- 3.7.8 FMECA – Failure Mode and Effects and Criticality Analysis
- 3.7.9 Process FMEA: Analyze and guide the development of new processes
- 3.7.10 System FMEA: High level review of failure modes
- 3.7.11 Design / Product FMEA: Specific analysis of failure modes around design
- 3.7.12 Subsystem FMEA
- 3.7.13 Component FMEA
- 3.7.14 Equipment FMEA
- 3.7.15 Automation FMEA
- 3.7.16 Design FMEA
- 3.7.17 Process FMEA
- 3.7.18 Service FMEA
- 3.7.19 Improvement FMEA
- 3.7.20 System FMEA
- 3.7.21 Global Types of Risk:
 - 3.7.21.1 Business/financial
 - 3.7.21.2 Human Factors – Patient & Machine Operator
 - 3.7.21.3 GxP
 - 3.7.21.4 CFR 21 Part 11
 - 3.7.21.5 Availability – Reliability & Maintainability
 - 3.7.21.6 Operational
 - 3.7.21.7 Measurement errors (Validity, resolution, bias, linearity, stability)
 - 3.7.21.8 Process integration
 - 3.7.21.9 Fabrication & Assembly
 - 3.7.21.10 Installation
- 3.7.22 Specific Types of Risk

- 3.7.23 Pharmaceutical GMP risk:
 - 3.7.23.1 Contamination (by equipment or operator)
 - 3.7.23.2 Inert material
 - 3.7.23.3 Dust
 - 3.7.23.4 Air pressure
 - 3.7.23.5 Micro-organisms
 - 3.7.23.6 Temperature
 - 3.7.23.7 Humidity
 - 3.7.23.8 Filter fibers
 - 3.7.23.9 Machine fluids
 - 3.7.23.10 Previous batch of pharmaceutical
 - 3.7.23.11 Inadvertent chemical transformation of product
 - 3.7.23.12 Reactivity
 - 3.7.23.13 Additive
 - 3.7.23.14 Absorptive
 - 3.7.23.15 Sanitation (capability of being cleaned & sanitized)
 - 3.7.23.16 Validation (capability of being validated)
 - 3.7.23.17 Maintenance (capability of being maintained at the validated state)
 - 3.7.23.18 Containment
 - 3.7.23.19 Calibration (capable of being calibrated/verified)
 - 3.7.23.20 Inspection (capable of performance being checked)
 - 3.7.23.21 Uncontrolled/unauthorized alteration of electronic records
 - 3.7.23.22 Electronic Data Control (No Unauthorized Access/
3.7.23.23 Alteration/Deletion)
 - 3.7.23.24 Audit Trails (Signatures, Dates/Times)
 - 3.7.23.25 Security (Potential Data Loss/Corruption & Backup)
 - 3.7.23.26 Accuracy of machine generated data, including calculations
 - 3.7.23.27 Access controls
 - 3.7.23.28 Data corruption/alteration/loss/security
 - 3.7.23.29 Backup data file maintenance and security
 - 3.7.23.30 Backup of any control software/firmware
 - 3.7.23.31 Validation records
 - 3.7.23.32 Revision change control & re-validation records
 - 3.7.23.33 Security
 - 3.7.23.34 Control of access

- 3.7.23.35 Backup
- 3.7.23.36 Audit Trail (record of changes, authorization and date)
- 3.7.23.37 PLCs/Firmware
- 3.7.23.38 Interfaces to other systems (SCADA) for transferring information
- 3.7.23.39 Revision control records
- 3.7.23.40 Control of access
- 3.7.23.41 Backup
- 3.7.23.42 Audit Trail (record of changes, authorization and date)
- 3.7.24 Availability Risk:
 - 3.7.24.1 Personnel: Are you able to find & attract the right employees to maintain your operations?
 - 3.7.24.2 Raw Materials / API: Are you able to secure qualifiable RMs or contracted product?
 - 3.7.24.3 Funding: Are your investors savvy enough for the business; do they have deep enough pockets?
 - 3.7.24.4 Business Capacities: Are you able to keep up with market demand for your product? Is the market able to keep up with your need to grow?
 - 3.7.24.5 Quality System: Is your Quality System able to provide enough flexibility to your manufacturing to allow for JIT operations?
 - 3.7.24.6 Measurement Error Risk:
 - 3.7.24.7 Validity: Are you measuring what you want to measure?
 - 3.7.24.8 Resolution/Discrimination: Can the measurement system detect small changes in the characteristic under study? Must be able to discriminate at least 1/10 of the normal process variation.
 - 3.7.24.9 Bias: Is your measurement method on target/accurate or does it overestimate or underestimate the true value of the characteristic?
 - 3.7.24.10 Stability: Does your measurement device tend to drift over time (fatigue, calibration)?
 - 3.7.24.11 Linearity: Is your device more accurate on one end of the scale than the other?

3.7.25 **Process risk:**

- 3.7.25.1 Variability of inputs to the machine
- 3.7.25.2 Raw materials
- 3.7.25.3 Utilities – Air, water, electricity, vacuum, etc.
- 3.7.25.4 Upstream/downstream equipment
- 3.7.25.5 Methods of operation
- 3.7.25.6 Ambient environment – temperature & humidity
- 3.7.25.7 Validation of the customer facility
- 3.7.25.8 Qualifications along the Supply Chain
- 3.7.25.9 FDA approval of the product/facility
- 3.7.25.10 Cycle time greater than or less than Takt time Takt Time – Available working time per day (minus breaks & scheduled downtime) divided by customer demand.
- 3.7.25.11 One piece flow (cycle time matches that of upstream/downstream processes)
- 3.7.25.12 Operator competence / training
- 3.7.25.13 Customer maintenance
- 3.7.25.14 Cleaning/sterilization
- 3.7.25.15 Process scale up

3.8 Engineering Review

- 3.8.1 Aveta has the capability to perform engineering reviews at any point along the drug development lifecycle. As well as review of the client's design elements, Aveta has the capability to assess and guide engineers and scientists in lean & analytical methodologies to optimize existing or create new processes. Following are some of the engineering review / assessment that Aveta can perform:
- 3.8.1.1 Facility Design: Review the design as built or to be built as provided by the architect and facility structural, mechanical, electrical, and fire life–safety engineers against the criteria defined within the BOD, any relevant URS documentation, and GAMP / GMP compliance including Change Controls and discuss and / or provide a report identifying any deficiencies or errant design.
 - 3.8.1.2 Process & Product Design: Scientific rationale & supporting data, process flows, P&ID's, product recipes, master batch records, representative batch records, product data, key performance metrics if available, results of any analytical

- work, product test results, any optimization work (including Change Controls) and discuss and / or provide a report identifying any deficiencies or errant design or process(es).
- 3.8.1.3 Automation Design Review all the relevant GMP / GAMP documentation of the URS, FRS, DDS/SDS/IDS, trace matrix, design documents, any analytical run data, FAT, automation/equipment validation, Change Controls, eBRs, cleaning validation, process validation, etc. and discuss and / or provide a report identifying any deficiencies or errant design or process(es).
 - 3.8.1.4 Equipment Design: Review all the relevant GMP documentation of the URS, FRS, DDS/IDS, trace matrix, design documents, any analytical run data, FAT, equipment validation, Change Controls, cleaning validation, process validation, etc. and discuss and / or provide a report identifying any deficiencies or errant design or process(es).
 - 3.8.1.5 Device Design: Process rationale & supporting data, process flows, P&ID's, product recipes, master batch records, representative batch records (or eBR print outs), product data, key performance metrics if available, results of any analytical work, product test results, any optimization work (including Change Controls) and discuss and / or provide a report identifying any deficiencies or errant design or process(es).
 - 3.8.1.6 Utility & Clean Utility System Design: Review all the relevant GMP / GAMP documentation of the URS, FRS, DDS/SDS/IDS, quality specs for utility, trace matrix, design documents, analytical testing of utility, equipment / system validation, Change Controls, BMS/EMS & control design, cleaning validation (where applicable), etc. and discuss and / or provide a report identifying any deficiencies or errant design or process(es).
 - 3.8.1.7 Environmental Exposure and Personal Protective Equipment (PPE): Review of list of possible raw materials, API & products that will be produced manufacturing facility; review of existing PPE plan to correlate the products to be manufactured with international standards of compliance per all cGMP and safety requirements.

3.8.2 If during the review / investigations any process or product problems arise, or if there are already identified any process or product stability issues, We will discuss with the client those problems to define a follow-on scope of work to trouble shoot and/or repair any deficient / errant process(es) or items.