



NCS Pharmaceuticals

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INTRODUCTION

NCS Pharmaceuticals, LLC. ("NCS") has a complete service A&E division, which provides consulting, engineering design, commissioning, validation/qualification services to the pharmaceuticals, biotechnologies, and medical devices industries. We provide validation services independently or in conjunction with engineering design, commissioning operations in order to optimize project cost and time. "Our commitment is to your success." NCS has a very much diversified well balanced team of resources. NCS' engineers, validation engineers/validation specialists are highly qualified and industry expert. Minimum requirement to be qualified as an engineer/validation engineer, validation specialist in our organization is BS in engineering/science, and considerable amount of experience in the industries. The most of the employees are certified professionals, holding graduate degrees in engineering/science and many years of industry experience. We have a flat organizational structure, which helps us to minimize cost, and maximize efficiency. Because of our well diversified resources, we utilize comparative advantage, and provide the best quality services at the lowest cost.

NCS provides services locally and internationally. Employees are familiar with the local and international regulations and current industry standard practices. NCS opens local offices, which work closely with the clients, and managed by the local representatives. The global head quarter in Somerset, New Jersey, USA, communicates with the local offices on a regular basis, and supports. NCS personnel include an international group of individuals, and NCS has aggressively sought to "cross train" the various offices allowing each individual to acquire international experience.

In order to meet the needs of our clients, NCS Pharmaceuticals has established Global Corporate Headquarters, located in Somerset, New Jersey, USA. The office is responsible for providing services in consulting, design, commissioning, validation and regulatory compliance needs globally. The office is currently managed by Dr. Nikhil Saha.

NCS understands that only the service organization capable of providing consistently the best quality services would survive in the competitive consulting marketplace. NCS hires only the best individuals who are motivated self-starters with proven skills. In order to maintain the best quality competitive resources, NCS has implemented an internal enrichment program whereby the best expertise within the company is transferred to all members. In addition, NCS regularly sends the personnel to in-house and external training sessions to provide training for all individuals on the current issues for the industries. We staff every project with a group of individuals with diverse right experiences so that we can provide our clients with the best quality services.

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RESOURCES

The goal of NCS Pharmaceuticals is to provide consistently the best quality services to the clients. We recognize that the foundation of this commitment is our people and we believe that people are our the most important and valuable asset. Currently, NCS employs seasoned veterans with diversified backgrounds. We are committed to hiring only those individuals with proven talent, so that each employee arrives at NCS with significant accomplishments to their credit. Since we hire only highly motivated individuals, we can be certain that each individual shares our commitment to improvement. Our continual improvement program begins with each individual. With diversified backgrounds, we believe that each individual can add to the education of everyone in the organization.

The training continues with formalized training programs. NCS has formalized training programs which provide our employees to become familiar with the successful methods being implemented at other projects and to learn from the in-house expertise of current industry standards and practices. NCS personnel are also encouraged to attend external conferences, classes, and trade shows for specific areas of interest or to better serve their clients.

We understand that each job provides the most useful training of all: experience. We guide the careers of our employees to ensure that each individual receives the experience which allows them to grow and maximize their potential. With this diverse and expert workforce, NCS is able to staff projects with proven talent to match a client's critical needs.

SERVICES

NCS Pharmaceuticals provides Consulting, Engineering Design, Commissioning, and Validation services separately or in conjunction with all to optimize the project cost and time.

NCS Pharmaceuticals has experience in engineering design, commissioning and validation in a wide variety of different facilities, systems, processes and equipment. This experience includes, but is not limited to the following:

<u>Facilities</u>	
Compounding/Formulation	Environmental Rooms
Aseptic Suites	Containment Areas
Laboratories	Medical Devices
Controlled Substances	Barrier Technology
BMS	



Utilities/Services	
Purified Water Water for Injection Sterile Air Compressed Air Plant Air Nitrogen Dust Collection Waste Neutralization	Process Chillers HVAC Vacuum Clean Steam Plant Steam Emergency Power Sterilize in Place Clean in Place

Systems/Computer Validation	
Computer Hardware Computer Software Automated Warehouse SAP LIMS	Label Control Automatic Inspection Distributed Control Systems Programmable Logic Controllers Decontamination System

Parenterals	
Steam Sterilization Depyrogenation Ovens/Tunnels Aseptic Filling/Processing Terminal Sterilization Radiation Sterilization Lyophilizers Form/Fill/Seal Machines Glassware Washers/Dryers	Environmental Monitoring Stopper Washing/Sterilizing Stoppering/Crimping Ethylene Oxide Sterilization Sterile Filtration Laminar Flow Hoods Inspection Stations

Oral Solid Dosage Forms	
Blenders High Shear Mixers Fluid Bed Granulators Milling Equipment Check Weighers Tablet Presses	Tablet Coaters Tablet Printers Capsule Printers Dryers Centrifuges Microwave Drying

Biotechnology	
Master Cell Banks Media Preparation Buffer Preparation Fermentation Harvesting Separation	Ultrafiltration Chromatography Biosafety Cabinets Deactivation Neutralization Sterilization



Bulk Pharmaceuticals	
Reactors Centrifuges Distillation Columns Crystallizers Extruders	Tank Farms Solvent Recovery Vessels/Agitators Filtration Drying

Packaging	
Unscramblers Fillers Pluggers Cappers Tamper Evident Features Labelers Batch/Date/Bar Coders Blister Packers	Neck Banders Accumulation Tables Cartoners Shrink Wrappers Overwrappers Case Sealers Palletizers Cottoners

Clients Served:

- | | | |
|---|--|---|
| <ul style="list-style-type: none"> ● Pfizer ● Schering-Plough ● Lilly ● Genentech ● Dupont ● Sidmak/Pliva | <ul style="list-style-type: none"> ● Wyeth ● Organon ● BMS ● DPT Labs ● Miwon | <ul style="list-style-type: none"> ● Merck ● Ortho-McNeil/J&J ● Amgen ● CBL ● Bio-Matrix/Genzyme |
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In addition to the NCS Pharmaceuticals experience sheets, NCS Pharmaceuticals Validation Services, provide services in the following areas:

- Start-Up
- Regulatory Compliance Consulting
- Quality Assurance Programs
- Process and Cleaning Validation
- Computerized Systems Validation
- Audits, etc.



PROJECTS:

API: We provided engineering design (estimates, vendor selections, specs, drawings-PFDs/P&IDs, bid evaluation, etc.), commissioning and validation services for active pharmaceutical ingredients (API) manufacturers. We managed the process validation, cleaning validation, and equipment/utility qualification for API manufacturers. Supported the clients with cleaning validation acceptance criteria and company-wide master plans and policies. Prepared and executed cleaning validation protocols and final reports. Responsible for the cleaning validation activities of reaction trains, centrifuges, tray dryers, rotary dryers, mills and blenders. Led a multi-discipline team to evaluate and improve all aspects of the cleaning validation program including residue limits, cleaning processes, documentation, and analytical methods validation. Prepared and executed equipment qualification (IQ/OQ) protocols and final reports for rotary vacuum dryers, vacuum tray dryers, stills, reactors, condensers, distillation columns, mills, blenders, hydrogenators, HVAC systems, BMS, softwall enclosures, crystallizers, and centrifuges. Prepared and executed process validation protocols and reports for crystallization, drying, milling and blending operations for API's and their intermediates. Developed, Computerized Systems Master Validation Policy. Assessed FDA compliance status of computerized systems, ranging from analytical systems in the QC laboratory and SCADA, DCS, and HVAC systems, to databases, maintenance management, and QA information systems. Developed validation plans, assessment scripts, specifications, procedures, manuals, schedules, and budgetary estimates. Assembled life cycle documentation, reverse-engineered, and enhanced SCADA system for product dryers to provide compliance with 21 CFR Part 11 by implementing a SQL Server based audit trail, electronic signatures, and a custom batch reporting system. Installed dryer system upgrade, wrote test scripts, and cataloged changes in a report for change control closeout. Developed prototype for a Part 11 compliant client-server solution to manage training records, coordinate with legacy personnel record management system, and eventually automate employee and HR notification of training requirements via e-mail. Prepared SOPs for cleaning validation, process validation, equipment qualification, master planning, and computer validation.

Solid Dosage: Provided engineering design, commissioning and validation services for solid dosage facilities. Generated/executed protocols and final reports for Quadro Comil, Stokes Granulator, AMF Mixer, PK Blenders, Ribbon Blender, Stokes Vacuum Dryer, Williams Tablet Conveyer, H&K Encapsulator, Mocon Vericaps, Pro-Quip Inspection Belt, Key Capsule Polisher, Metal Detector, Stokes Sugar Coating Pan, Coating Solution Tank, and PIAB Pneumatic Tablet Transfer System.

Mammalian Production: Provided detailed design for cell culture pilot plant. Involved with start-up and commissioning, and validation of automated centrifuge with CIP/SIP, clean gas systems, plant control system, plant/clean steam, USP Purified Water, WFI, cooling tower water, and plant/process chillers. Prepared validation turnover packages, generated/executed validation protocols and reports for cooling tower water, reverse osmosis water, WFI, USP Purified Water, HVAC clean gases, plant control systems, ultrafiltration skids, depth filter housings, CIP skids, B. Braun bioreactors, buffer tanks, media tanks, chromatography skids, column packing, autoclave, glass washer, centrifuges, pumps, filters, cold rooms, freezers, refrigerators, and incubators.

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Clinical Production: Provided services to the clinical manufacturing facilities. Directly involved with start-up and commissioning of process control system, HVAC, UPS, clean compressed air, plant/clean steam, USP Purified Water, plant/process chillers, process tanks, incubators, shakers, fume hoods, biosafety hoods, laminar flow hoods, and bio-waste system. Prepared validation turnover packages, generated/executed validation protocols and reports for process control system, HVAC, clean compressed air, clean steam, USP Purified Water, incubators, and process tanks.

Cell Culture: Provided services in design, commissioning and validation for the bioreactors projects. Prepared validation master plan for project. Prepared and executed equipment qualification (IQ/OQ) protocols.

Contract Packaging and Contract Manufacturer: Developed cleaning validation and packaging validation programs including preparation of the validation master plans, preparation of SOPs, and development of the validation protocols. Did audit including the areas of cleaning validation, process and packaging validation, process equipment, HVAC, filling machines, control systems, and utility systems, and laboratory systems qualification. Provided design, start-up, commissioning and validation for contract research organization and contract manufacturers. Supported the installation of packaging equipment for the manufacture of an insulin metering system. Performed start-up, commissioning, and validation (IQ/OQ) activities for EAM Filter/Capper, Chromatography Systems, EAM Cartridge Assembly Machine, Comas Plunger/Insert Assembly Machine, Cazzoli Gross Washer with Siliconization, Cazzoli Stopper Washer, Receiving Vessels, and Formulation Vessels, Lab Equipments, etc. Developed and executed depyrogenation protocols. Prepared SOPs.

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PROJECT MANAGEMENT

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NCS believes that the success of any project is strongly dependent upon the project management; schedule, cost, and manpower. The following is a typical NCS approach to project management, but not limited.

A. PROJECT KICK-OFF & TEAM BUILDING

It is the experience of NCS Pharmaceuticals that a project team building session should occur during the kick-off meeting with all parties. We believe that this is essential for a successful project execution. A typical team-building meeting includes:

- Establishing mission
- Establishing roles and responsibilities
- Setting measurable goals, objectives, and definition of success
- Focus efforts on attaining goals

At the kick-off meeting, NCS Pharmaceuticals presents a schedule for client review. The schedule contains project milestones, identifies the critical path, and clearly indicates client process personnel requirements and turn around times. It is assumed that all standards, protocols are formatted in conjunction with NCS and client standards and procedures. Typically client provides all applicable standard operating procedures and identify and schedule all necessary training for NCS personnel. The NCS Pharmaceuticals Project Manager assigned to the project, leads the kick-off meeting.

B. PROTOCOL GENERATION AND APPROVAL

Usually, protocol templates are established in conjunction with NCS and client standards, which are the basis for each of the subsequent protocols generated by NCS Pharmaceuticals for the various equipment/systems. NCS Pharmaceuticals may add/change the content of these documents based on current industry standards and our technical expertise, but will not delete any portion without prior authorization by the client. NCS Pharmaceuticals expects that an equipments/system file and all necessary engineering documents will be available to allow for ample time for protocol generation. Draft and final protocols are provided throughout the project for client review/comment/approval. All draft and final protocols are transmitted via a transmittal cover page. It is the responsibility of the NCS Pharmaceuticals Project Manager to log and track all documents transmitted to the client to insure timely review cycles and approval in order to meet the project schedule. Changes to draft protocols should be returned to NCS Pharmaceuticals within five (5) business days. Draft protocols are then changed based on the client comments and final protocols are issued to the client for approval. It is assumed that the client will approve each submitted protocol within five (5) business days of receipt. Approval of each protocol is required prior to any qualification activities (execution) for that specific system or equipment. Delays in the protocol review and approval process could impact the validation schedule and, as such, should be kept to a minimum. As time is of the essence on any project, mutual cooperation for the submission, turn around, and approval of protocols is very crucial for maintaining schedule and minimizing project overruns.

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C. PROTOCOL EXECUTION

It is NCS Pharmaceuticals intent to qualify/validate the equipment/systems associated with the project in a rapid and efficient manner and in full compliance with cGMPs. It is assumed that the construction/procurement documentation for the equipment/systems is available. In this way NCS can appropriately assign its resources so as to eliminate any inefficiencies and downtime. It is assumed that during the execution, client operators will be available where necessary to operate the equipment/systems according to SOP. In this way, the equipment is operated within a “state of control” and assures more accurate and reliable results. In addition, vendor assistance may be required. Any sampling and laboratory testing is the responsibility of client personnel. Final reports generation is initiated following the completion of qualification/validation activities for each system/equipment. Deviation reports are delineated and addressed within the body of the final report. The reports will follow the client standard format, or can be established in conjunction with NCS and client standards.

D. PROJECT MANAGEMENT

The NCS Pharmaceuticals project manager:

- Coordinates the work of consultants engaged by NCS Pharmaceuticals and the client.
- Develops and maintains a detailed schedule for NCS Pharmaceuticals work on the project. The schedule is broken down by phases (preparation, execution, final reports, etc.), by equipment/system, and clearly defines client activities. The schedule is updated as required and is included in the monthly progress report.
- Conducts weekly coordination meetings, which include all team members including the construction manager, engineering project manager, and client representatives, as applicable. The primary focus of the meeting is to address key issues, coordinate activities, and communicate status. The meeting also addresses schedule status, cost status, and scope changes. Minutes of the meeting are generated/distributed in a timely fashion.
- Issues a monthly progress report. The report includes an executive level summary of project progress, status, problems, and objectives. The report also includes information regarding schedule status, summary of progress to date by system, summary of cost information with reference to budget and projection of final costs. A detailed analysis of any deviations in cost and schedule from the previous report is also included. If applicable, the report includes status with respect to cost and schedule on any procurement activities for which NCS Pharmaceuticals is responsible.
- Reviews, comments, and supplements (if necessary) the validation master plan (as applicable).
- Reviews all protocols, executions, and final reports prior to submittal to the client for review/approval.

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E. PROJECT MANAGEMENT TOOLS

In addition to the project schedule and cycle report, the following project management tools are also used to track/report status.

Action Items Report: Action items are identified and monitored to insure prioritization of protocol preparation, timely gathering of required documentation (specifications, drawings, manuals, etc.), and review/approval cycles. A champion is assigned to each action item. Action Items reports are generated weekly or as deemed necessary.

Protocol Execution Status: Each system/equipment is assigned a champion who will be responsible for the execution of the protocol(s) associated with that system/equipment. It is the responsibility of the champion to communicate to the project manager the status of protocol execution on a weekly basis. These weekly reports are the basis upon which the project manager determines overall percent complete for the project.

Work Breakdown Structure: A project work breakdown structure (WBS) can be created for the project that divides the project scope into discrete manageable work packages that focus on the deliverables included in the project scope of work. The WBS has a coding structure that is logical and permits tracking of progress, costs, and work hours.

Change Management: The agreed to scope of services establishes the control base for trending changes in cost. Changes in the scope of work or other cost/schedule changes are approved in writing before any work is executed. A Change Control form is used to document identified changes and the associated cost. The form is completed by the Project Manager and is submitted to the client for approval. Once the change has been approved, the original estimate is adjusted to reflect the current estimate. Changes are also reflected in the schedule. The Project Manager maintains a Change Order Log, which is included in the monthly report.

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PROJECT COMMISSIONING AND QUALIFICATION GUIDELINE

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1. INTRODUCTION

This document contains guidelines for commissioning and qualification of manufacturing systems installed or modified via capital projects. All facilities, equipment, and utilities in manufacturing sites will be commissioned in accordance with Good Engineering Practices, and those systems and components determined to have a direct impact on product quality will be qualified in accordance with the regulations set out in United States Food and Drug Administration (USFDA) current Good Manufacturing Practices (cGMP). This document uses the framework provided in the ISPE Commissioning and Qualification Baseline Guide.

2. PUOPOSE

This guideline is established to provide a consistent approach to commissioning and qualification activities for capital projects executed NCS Pharmaceuticals (NCS). All commissioning and qualification activities should be planned, coordinated, documented and executed in an efficient manner, utilizing the procedures, templates, and other documentation referenced by this guideline.

The foundation to achieve this objective is based on the following principles:

- Mechanically complete and commission all systems using Good Engineering Practices.
- Document the mechanical completion and commissioning of systems to permit the integration and cross-reference of test documents through all phases of the project life-cycle to maintain quality assurance focus and to minimize duplication of testing.
- Perform an impact assessment: Only direct impact systems and their critical components will be subject to qualification activities, procedures, and documentation. Indirect and No impact systems will be commissioned only.
- Organize summary reports by system to rationalize the number of reports to be written, reviewed and approved.
- Limit the number of document approvers to the essential personnel, and define their role in the approval process.
- Determine the relevant procedures for each project (i.e. not every procedure is required for every project).
- Plan commissioning and qualification activities at the appropriate project life-cycle stage.
- Provide a mechanism for determining commissioning and qualification activities by project phase and deliverable.
- Provide the appropriate documented evidence to support the required level of equipment, facility, and utility qualification.

3. SCOPE

This Commissioning and Qualification Guideline applies to projects supporting new and renovated pharmaceutical manufacturing operations. The resulting documentation forms part

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of the requirements for the site or facility-level master validation plan. This Guideline document focuses on the engineering approaches and practices involved in providing cost effective manufacturing facilities in a timely manner that meet their intended purposes. Specifically, it addresses the process of completing, commissioning and qualifying the facilities, utilities, equipment, and systems regulated by the USFDA and appropriate Global agencies. This document is not intended to address Computerized System Validation, on-going maintenance, and Cleaning Validation or Product/Process Validation. These items are covered under separate documents.

4. RESPONSIBILITIES

Site Engineering Leaders are responsible for the implementation of this guideline. Site Level Quality Assurance or Validation Leadership is responsible for review and approval of documents as outlined in the guideline, and for monitoring performance against this guideline. The list of commissioning and qualification documents requiring QA/Validation Approval, refer to section 6.6 of this Guideline.

The specific responsibilities for effective completion of commissioning and qualification tasks are described in the relevant sections of this guideline and referenced procedures.

5. ORGANIZATION AND USE OF THIS GUIDELINE

The ISPE Commissioning and Qualification Baseline Guide provides the general framework to this Guideline and the approach that NCS has adopted to Commissioning and Qualification (C&Q). As such, this Guideline is organized in the same general chapter/content arrangement as used in the ISPE Guide.

The key principle embodied in this guideline is use of pre-formatted templates to plan, document, and execute the various commissioning and qualification tasks within a project. Template-based documentation will meet the NCS goal of consistently applied Commissioning and Qualification practices, and will support cost-effective project execution by reducing duplication of effort.

Each template is accompanied by an associated procedure, explaining its use. Additionally, some effort has been made in providing specifically formatted templates for certain types of systems commonly used at NCS (for example, Purified Water). While not all-inclusive, this library should assist users in developing cost-effective C&Q documentation for many projects.

Anticipated users of this Guideline include:

- NCS Project Managers and Engineering Leadership
- Quality Assurance and Validation Managers
- Contracted engineering and validation support firms

1. The Commissioning and Qualification process extends throughout the project lifecycle, from the Conceptual Design Phase (e.g. User

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Requirements Spec) through construction (e.g. Factory Acceptance testing), Commissioning, Qualification, and turn-over. Users should refer to this Guideline at each project stage to determine the appropriate C&Q activities to be executed (see section 6).

This Guideline and related documents can be accessed electronically via the NCS Global Engineering web page.

5.1 Definitions & Abbreviations

A key requirement for consistent C&Q practice is the adoption of a standard set of terminology. For a full listing of commissioning and qualification terms, definitions, and acronyms, refer to the NCS Glossary of Commissioning and Qualification terms. This document is intended to provide all users with a common language for Commissioning and Qualification Activities.

6. OVERALL COMMISSIONING AND QUALIFICATION APPROACH

Good Engineering Practice is essential to the system completion, commissioning and qualification activities. Good Engineering Practice, commonly referred to as GEP, is a set of proven and accepted, cost-effective engineering methods and practices that ensure the effective satisfaction of end-user requirements. Guidance and standards that have been defined by engineering institutes and other learned bodies support GEP. These standards and approaches are defined in procedures, check sheets and templates to be utilized for the systems checkout and commissioning for all systems. For systems having a direct impact on product quality, GEP is supplemented by enhanced documentation and qualification practices with the active participation of Quality Assurance (QA) and/or Validation personnel.

Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) are activities that global regulatory agencies may have an interest in, since these are the final activities before process validation can begin. IQ/OQ/PQ requires enhanced documentation, QA involvement and additional tests and checks known as Qualification Practices. These practices are carried-out through the project protocol and report documents, associated tests, and supporting procedures and guidelines.

The system completion, commissioning and qualification approaches are briefly described in the following sections. More details concerning each phase of the project can be found in the corresponding procedure individually covering each item.

6.1 Commissioning Activities

Commissioning requires timely planning, documentation, and managed resources and encompasses much of the start-up activities of a project's life cycle. Commissioning includes the following 3 phases:

- A) Inspection and Testing: This phase includes such steps as hydrostatic testing

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of piping, visual inspections, grounding / bonding checks, electrical continuity, motor meggar checks, non-destructive weld examination, etc. This step is intended primarily to establish that the system has been physically installed as per the design documents. This step is characterized by a “power off” state, and is primarily executed by the construction contractors as a required step in completing their scope of work.

At the completion of this first commissioning step, the system is considered Mechanically Complete. This significant project milestone represents the completion of the contractor’s scope of work, and recognizes that sufficient inspection and testing have been completed to verify conformance to the design/construction documents.

B) Regulation, Adjustment, and Setting To Work: This phase involves the process of calibration and preliminary adjustment of instruments, sensors and mechanisms before initial energizing of systems, to operate within the required tolerances. This includes activities such as instrument calibration, control system loop checks for instrumentation, motor rotational checks, laser alignment, lubrication, balancing of chilled water and air conditioning systems, and the adjustment of a reject mechanism on a packaging line. This step is characterized by a “power on” state, and is primarily executed by technicians and specialty contractors to prepare the system for its run test.

C) Functional/Run Testing: This phase includes testing to demonstrate that the system and interdependent system components deliver the required capacity or duty. These tests may involve full operational testing throughout anticipated ranges, but are not conducted with product (eg: water run or a run on an excipient/surrogate). This step is intended to “shake-down” and test systems fully prior to turn-over to the system owner, either for manufacturing (indirect and no impact), or for Qualification (direct impact).

6.2 Qualification Practices

For direct impact systems, Good Engineering Practice will be enhanced and supported by Qualification Practices to meet the compliance needs of businesses regulated by FDA and other regulatory authorities.

Qualification Practices include:

- System Impact Assessment (evaluation of which systems require qualification and why, and which system do not, and why)
- Active Participation of the Quality Assurance and/or Validation groups
- Enhanced Design Review
- Enhanced documentation, document management and a structured approval process
- QA Change control



- Greater end user participation
- Qualification plans, protocols, and reports to facilitate the verification and testing, and provide the recorded data and documentation supporting the verification and testing.
- Training

6.2.1 Impact Assessment

This is the process of determining which systems and/or system components should be subject to Qualification Practices in addition to Good Engineering Practices (GEP) and which systems should be commissioned in accordance with GEP. The assessment is initially performed by evaluating the impact that a system has on the quality of the product. After the system level assessment, the components of the system are later evaluated to determine if they are critical to establish or maintain the quality of the product. The appropriate Qualification Practices are then applied to the “Direct Impact” systems and critical components, while the “Indirect Impact” or “No Impact” systems and their components shall be designed, installed and commissioned according to GEP. Following this approach, the appropriate effort and focus can be maintained on the quality impacting systems and components.

6.2.2 Active Participation and Early Involvement of Quality Assurance and/or Validation

Early Quality Assurance and/or Validation group involvement should provide for clear communication of regulatory requirements, ensuring that procedures and practices are established up front for incorporation into the project. The goal is for the quality unit to work in partnership with engineering and other functional support groups involved with the project for a smooth, efficient hand-over, in compliance with regulatory expectations.

6.2.3 Enhanced Design Review

The approach that NCS has adopted is that the Enhanced Design Review process will be used as a tool to help meet the expectations of regulatory authorities having jurisdiction over US manufacturing sites. This Guideline has adopted two structured design review steps to satisfy the Enhanced Design Review process as recommended by the ISPE Baseline Guide.

A) cGMP and GEP check-list review

B) User Requirements spec review

Both reviews are typically performed during the Preliminary Design Phase of a project, and are documented in the Enhanced Design Review Summary Report. Note that this summary report can be used to satisfy the requirements of Design Qualification (DQ) as per Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,



where required.

6.2.4 Enhanced Documentation

The document requirements for a project are listed on a Turnover Package Matrix or “TOP” Matrix. The matrix lists the systems identified across the top of the matrix, and the list of project- documents down the side. The project team completes this list for the project to ensure that the documentation requirements are communicated to suppliers, construction management (CM), and contractors for proper and timely delivery in the project. The project TOP matrix defines all documentation requirements for the project, and defines their inclusion in one of the three (3) final turnover packages: 1) System Owner, 2) Facility Maintenance, and 3) Site Archive. Note that the Site Archive is the most comprehensive of the 3 TOP’s, and typically includes all documents.

Enhanced Documentation is that portion of the Archive TOP that specifically applies to Direct Impact Systems, and typically includes protocols and other Qualification Documents as defined in this Guideline.

6.2.5 QA Change Control

Appropriate documented change control should exist through the life of the project, and in the long-term maintenance of qualification after the completion of the project. In the early stages of a project, through design, construction and commissioning, changes are handled by Engineering following guidance set forth in Good Engineering Practices (GEP). Quality may not be routinely involved in the engineering change management process, as these changes are typically linked to technical management of the project. However, the engineering change management system should allow for Quality review and input into the change when one or more of the following conditions occurs:

- The change alters the Impact Assessment (i.e. it causes a formerly indirect impact system to now be a direct impact system or vice-versa).
- There is a fundamental change in the design concept or project scope
- There is a change in the User Requirements Specifications (URS)

6.2.6 Greater End User Participation

“Direct Impact” systems and interfaces demand closer and more comprehensive “hands-on” involvement from the End User team. Possible areas of involvement include:

- Supplier Audits
- Factory Acceptance Testing
- Commissioning execution



- Site Acceptance Testing
- Qualification Protocol execution

6.2.7 Qualification Plans, Protocols and Final Qualification Summary Reports

Qualification plans, protocols and final qualification summary reports are developed to provide instruction on the scope of the qualification activities, define the systems involved in the project, and provide testing descriptions and data to support the adherence to predetermined acceptance criteria. The Project Commissioning and Qualification Plan (PCQP) define the full scope of Commissioning and Qualification documentation to be developed for each project. Typical Qualification documents developed for a project include:

- Project Commissioning and Qualification Plan (PCQP)
- Installation Qualification Protocols
- Operational Qualification Protocols
- Performance Qualification Protocols
- Qualification Summary Reports

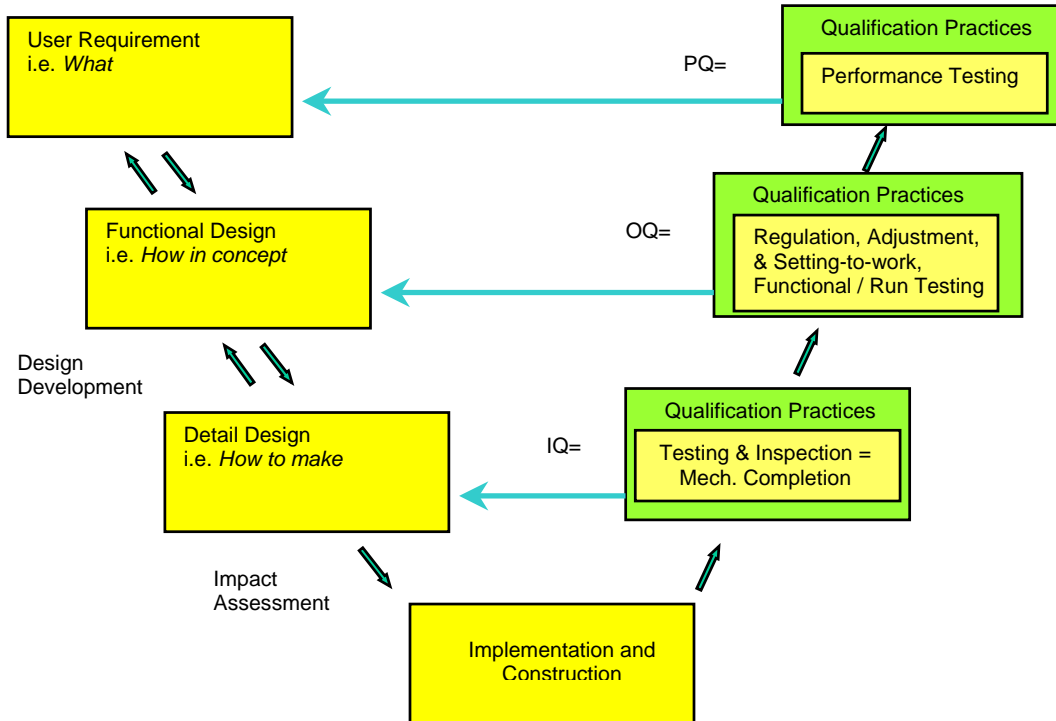
These documents are further described in the Procedure on Project Commissioning and Qualification Plans, the Procedure on Qualification Protocols, and the individual qualification activity procedures and templates.

6.2.8 Training

Training is a critical part of the cGMP compliance. Training should address overall qualification requirements and practices while referencing the regulatory significance. Training must be provided to those functional areas that will participate in the qualification activities, and those that will complete documentation directly supporting qualification activities. These groups include members of the project team, appropriate members of the contract engineering firm(s), and subcontracted personnel. Documentation should exist that describes the training contents, and records should be maintained of personnel to whom training was administered.

6.3 Relationship between Commissioning and Qualification: The V-Model

The relationship between commissioning and qualification can be best shown utilizing the “V-model” as shown below. The engineering design and implementation activities are down the left side of the “V”, while the system completion and commissioning activities are shown up the right side of the “V”. These activities are then “enveloped” or enhanced by qualification practices at each stage to satisfy the requirements for direct impact systems and their critical components in the IQ, OQ and PQ phases of the qualification effort.



6.4 Commissioning and Qualification Work Sequence:

The table on the following page gives the typical activities and deliverables associated with each phase of the project life cycle. This table should be used as a guide to ensure that all items are addressed, with responsibilities assigned for completion. The list should be used as a planning tool; the actual timing of the listed activities and deliverables may vary based on the unique needs of each project.



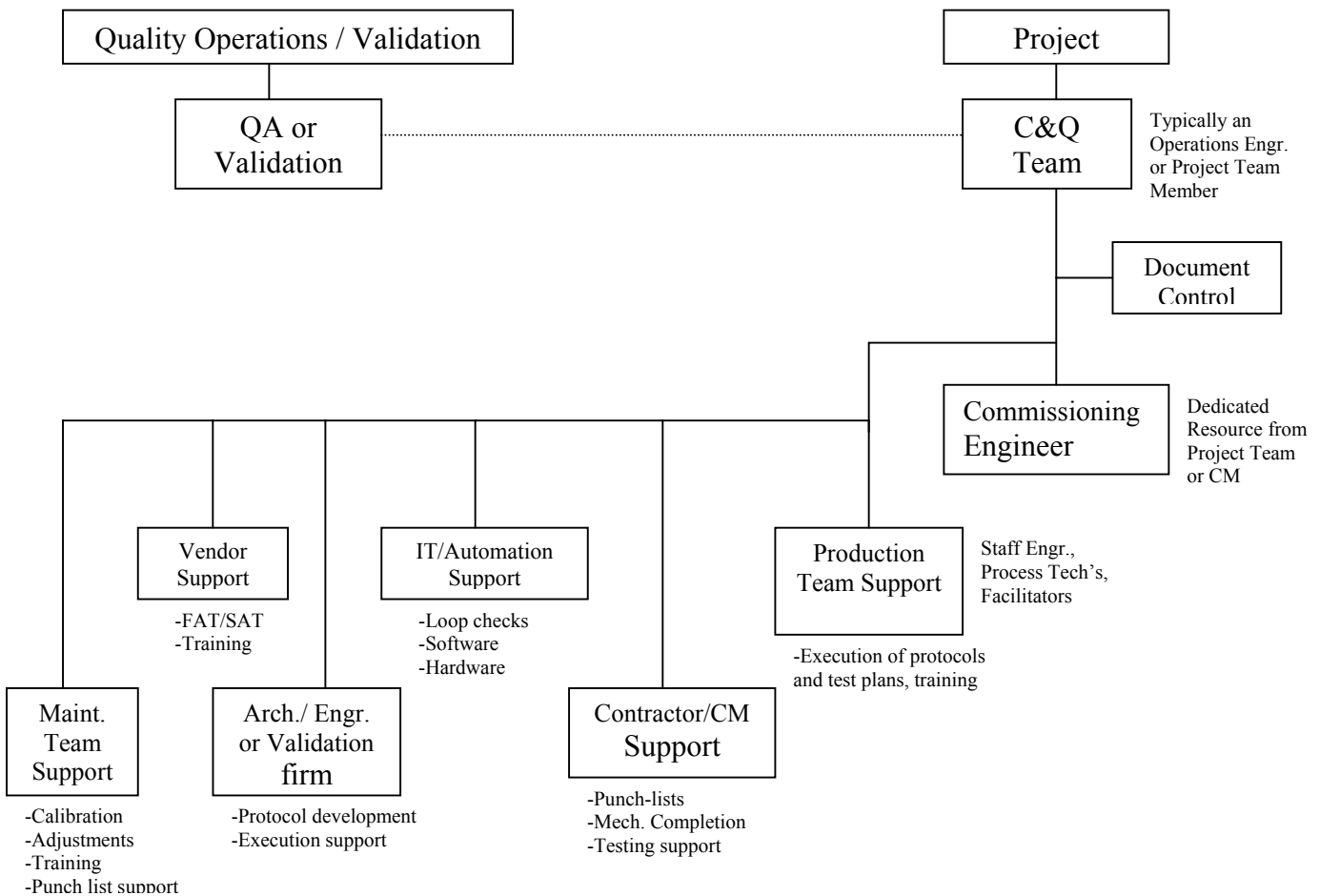
COMMISSIONING AND QUALIFICATION WORK SEQUENCE		
Activities	Deliverables	SOP
Conceptual Design Phase		
- Team Alignment/Kickoff		
- Review site policies, procedures and guidelines pertaining to commissioning and qualification.		
- Develop the Project User Requirements Specification	URS	
- Develop Design CPA	CPA	
Preliminary Design Phase		
- Develop system level impact assessment	Impact Assessment	
- Develop Master TOP Matrix	TOP Matrix	
- Develop Material & Equipment Inspection Plan		
- Establish the document review and approval process		
- Establish Engineering Change Control procedures		
Develop the PCQP- Referencing the following: - System Level Impact Assessment - Master TOP Matrix - Inspection Plan - Automation Commissioning and Qualification Strategy	PCQP	
- Update/Approve the Project User Requirements Specification	URS	
Enhanced Design Review: - cGMP/GEP Checklist Review - URS Review	-cGMP/GEP Checklist Review - URS	
Enhanced Design Review Summary Report	EDR Summary Report	
- Develop Definitive CPA	CPA	
Detailed Design Phase		
- Develop Detailed TOP Matrix	Detailed TOP Matrix	
Develop Protocols and Test Plans by System - Commissioning Plans – using library of commissioning check-sheets - Qualification Protocols – using library of pre-formatted IOQ protocol templates - SOPs - Training Plans - FATs (Plan)	Comm. Plans Qual. Protocols SOPs Training Plans FATs(Plan)	
- Perform Component Level Impact Assessment, including component numbering	Component Level impact assessment	
- Review PCQP based on Detailed Design development and update if necessary	PCQP Updated	
Procurement Phase		
- Procure C&Q Services	RFP for services	
- Pre-Qualify Vendors and Contractors		
- Agree on Mechanical Completion definition, contractor/vendor scope and turn-over definition for each system	(w/contract specs)	
- Ensure that documentation specifications, and commissioning and qualification requirements are included in purchase orders and contracts. Examples: o Include FAT/SAT Guideline in Equipment Specs o Include Post Construction Cleaning guideline requirements in equipment and contract specs o Include appropriate commissioning scope (including completion of check-sheets) in construction contract specs	(w/contract specs)	



COMMISSIONING AND QUALIFICATION WORK SEQUENCE		
Activities	Deliverables	SOP
Construction Phase		
- Vendor shop inspections per Inspection Plan (PDIs, etc.)		
- Conduct FAT inspections as per Inspection Plan		
- Perform material receiving & associated inspections		
- Compile and Assemble Turn Over Packages	TOP	
Commissioning Phase		
Execute Commissioning Test Plans, by system		
- Execute Inspection and Testing Phase		
- Mechanical Completion - Milestone		
- Execute Regulation, Adjustment, setting to Work Phase		
- Execute Functional Testing Phase, including SAT's	Executed Comm Plans	
Maintenance TOP Handoff	Maintenance TOP	
Execute Post Construction Cleaning		
Qualification Phase		
Execute Qualification Protocols by System		
- Execute IOQ Protocols	Executed IOQ	
- Execute PQ Protocols	Executed PQ	
Close Out Phase (Handover to PV and Manufacturing)		
Owner (Operations) TOP Hand-off	Owner TOP	
Develop Final Qualification Summary Reports	Final Qualification Summary Reports	
As- built updates of design docs by A/E	As Builts	
Archive TOP.	Archive TOP	
Handover to Manufacturing for process/cleaning validation		

6.5 Sample Commissioning & Qualification Team Organization- Supporting an Individual Project

The following sample represents a suggested organizational approach to staffing the C&Q effort for a typical project. Boxes may represent part-time, full-time, or simply support functions provided by another team.





6.6 QA/Validation Approval- Commissioning and Qualification Documents

The following tables describe the role of QA/Validation in the review and approval of commissioning and qualification documents:

Table 1: Documents Requiring QA/Validation Approval

Document Description	QA/Validation Role
User Requirement Specification (URS)	Approve the URS: Confirm appropriate PQs/Quality drivers have been considered and applied
Impact Assessment (System/Component)	Approve the Impact Assessment: Endorse system classifications and boundaries per the Impact Assessment Guideline
Project Commissioning & Qualification Plan (PCQP)	Approve the C&Q plan for the project
Enhanced Design Review/Design Qualification Summary Report	Approve the EDR Summary Report. Review/confirm that the process was followed and action items addressed.
Commissioning Test Plans & Reports (Direct Impact Systems Only)	Approve the Commissioning Test Plans and Test Reports. Review content, endorse that process was followed.
IQ/OQ/PQ Protocols (pre and post execution)	Approve protocols. Review content, endorse that the process was followed.
Final Qualification Summary Reports	Approve the Final Report and Qualification Status. Review content.



Table 2: Documents Not Requiring QA/Validation Approval

Document Description	Rationale
Engineering Drawings and Specifications	An engineering function
FAT and SAT Test Plans and Reports	FAT and SAT are steps within the commissioning process of a system.
Post Construction Cleaning Records	Post construction cleaning is a GEP step prior to cleaning validation.
Turnover Packages and Matrices	Records relating to regulatory compliance (Qualification Records) within the TOP are reviewed/approved by QA/Validation.
Commissioning Test Plans and Reports for Indirect Impact and No Impact Systems	Indirect and No Impact systems do not directly impact product quality and are commissioned as per GEP.
Vendor/Contractor Procurement Pre-Qualification Records	An engineering and procurement function, except where a corporate audit is required to establish qualification (e.g. Software)



REFERENCES

Code of Federal Regulations (1998), "Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs; General", 21, Part 210 and "Current Good Manufacturing Practice for Finished Pharmaceuticals", 21, Part 211.

ISPE Pharmaceutical Engineering Guides for New and Renovated Facilities, Volume 5, "Commissioning and Qualification". First Edition, March 2001

"Guidance for Industry, Q7Q Good Manufacturing Practice Guideline for Active Pharmaceutical Ingredients", August 2001, published jointly by US Dept. of Health & Human Services, US Food and Drug Admin, and Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and International Conference of Harmonization (ICH).

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SAFETY POLICY

This is NCS Pharmaceuticals' corporate safety philosophy and standards of operation, and it applies to all the project locations.

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SAFETY IN WORKPLACE: In order to provide a safe and healthy work environment for employees, customers and visitors, NCS Pharmaceuticals (NCS) has established a workplace safety program. This program is a top priority for NCS Pharmaceuticals. The senior level manager at each location has responsibility for implementing, administering, monitoring and evaluating the safety program. Its success depends on the alertness and personal commitment of all. NCS provides information to employees about workplace safety and health issues through regular internal communication channels such as employee meetings, bulletin board postings, memos or other written communications. Employees and supervisors receive periodic workplace safety training. The training covers potential safety and health hazards and safe work practices and procedures to eliminate or minimize hazards. Some of the best safety improvement ideas come from employees. Those with ideas, concerns or suggestions for improved safety in the workplace are encouraged to raise them with their supervisor, or with another supervisor or manager, or bring them to the attention of a member of the safety advisory group. All reports can be made without fear of reprisal. Each employee is expected to obey safety rules and to exercise caution in all work activities. Employees must immediately report any unsafe condition to the appropriate supervisor. Employees who violate safety standards, who cause hazardous or dangerous situations, or who fail to report or, where appropriate, remedy such situations, may be subject to disciplinary action, up to and including termination of employment. In the case of accidents that result in damage to property or injury, regardless of how insignificant the injury may appear, employees must immediately notify the Project Manager or the appropriate supervisor. Such reports are necessary to comply with laws and initiate insurance and workers' compensation benefits procedures.

ALCOHOL/DRUG MISUSE PREVENTION POLICY: The use of alcohol in the workplace, as well as being under the influence of alcohol while performing one's job, is prohibited. The program is summarized in this policy. The key points are covered. It is very important that every employee affected by this program read and understand this policy, since the consequences of violating the rules, may be the loss of one's job. The program's managers are the President, Individual Office and Divisional Managers of NCS. Please call them if you have any questions about the program set forth in this policy. All employees are subject to the provisions of this program. The term "covered employee" means any person who performs duties for NCS and the subsidiaries of NCS. Any Covered Employee is subject to the rules set forth here, while he or she is performing any work related function; just before he or she is to perform the function; and just after he or she has stopped performing the function. For example, someone who has not yet started his or her job but is ready to begin the job is subject to the rules.

DRUG AND ALCOHOL USE: This is NCS' desire to provide a drug free, healthy and safe workplace. To promote this goal, employees are required to report to work in appropriate mental and physical condition to perform their jobs in a satisfactory manner. While on NCS premises and while conducting business related activities off NCS premises, no employee may use, possess, distribute, sell or be under the influence of

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alcohol or engage in the unlawful manufacture, distribution, dispensation, possession or use of illegal drugs. Violations of this policy may lead to disciplinary action, up to and including immediate termination of employment and/or required participation in a substance abuse rehabilitation or treatment program. Such violations may also have legal consequences. The legal use of prescribed drugs is permitted on the job only if it does not impair an employee's ability to perform the essential functions of the job effectively and in a safe manner that does not endanger other individuals in the workplace. Employees with questions or concerns about substance dependency or abuse are encouraged to use the resources of the Employee Assistance Program. They may also wish to discuss these matters with their supervisor to receive assistance or referrals to appropriate resources in the community. Employees with drug or alcohol problems that have not resulted in, and are not the immediate subject of, disciplinary action may request approval to take time off to participate in a rehabilitation or treatment program through NCS' health insurance benefit coverage. Leave may be granted if the employee agrees to abstain from use of the problem substance; abides by all NCS policies, rules and prohibitions relating to conduct in the workplace; and if granting the leave will not cause NCS any undue hardship. Under the Drug Free Workplace Act, an employee who performs work for a government contract or grant must notify NCS of a criminal conviction for drug related activity occurring in the workplace. The report must be made within five days of the conviction. Employees with questions on this policy or issues related to drug or alcohol use in the workplace should raise their concerns with their supervisor.

ALCOHOL-FREE AND DRUG-FREE WORKPLACE POLICY: Illegal drugs in the workplace are a danger to all who work here as well as to our customers. They impair safety and health, promote crime, lower productivity and quality, and undermine public confidence in the work that is done. It is the policy of NCS to maintain a drug-free workplace in compliance with the federal Drug-Free Workplace Act and the Anti-Drug Program. All employees are absolutely prohibited from unlawfully manufacturing, distributing, dispensing, possessing, using or being under the influence of controlled substances in the workplace. These substances include, but are not limited to: marijuana, cocaine, opiates, phencyclidine (PCP), amphetamines, and alcohol. (The testing program described below does not include alcohol which has its own testing policy.) You must, as a condition of employment, abide by the terms of this policy and report any criminal drug convictions on or off NCS premises on NCS business within five (5) days in accordance with the Drug-Free Workplace Act. Any employee violating this policy is subject to discipline including termination.

DRUG TESTING RECORDS: NCS must maintain certain medical and statistical records in connection with its Anti-Drug Program. These records are sensitive and will be treated on a confidential basis. The reports required to be submitted and the methods of submitting those reports insure confidentiality. All information concerning employee drug testing results and rehabilitation information will be maintained in strictest confidence. Such information will be released to a third party only with the written consent of the individual involved with the exceptions provided by federal law. This Policy is intended to comply in all respects with the regulations of the DOT on anti-drug use, prevention and

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testing. To the extent that it does not or is subject to an interpretation that it does not, the above regulations together with any future amendments thereto take precedence. All amendments to say regulations to the extent that they mandate a change to the Policy shall become part of this Policy on the date said amendments become effective.

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