NICOLET™ ANTARIS™

Pre-installation Qualification Overview

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Chapter 1 ValPro Overview

ValPro™ is a system qualification package provided by Thermo Electron Corporation to assist users of our products in their system validation process. It includes tools and documentation to enable users to become compliant with FDA, cGMP, and other relevant regulatory guidelines. ValPro provides software, documentation, and traceable reference standards. ValPro also includes:

- Complete installation procedures, testing routines and documentation for Installation Qualification (IQ)
- Installation and instrument certification
- Complete manufacturer-verified instrument tests for appropriate system performance
- Pharmacopeial-recommended tests (where appropriate) for specific instrument performance
- Instructions for operation of all instrument tests, whether automated or manual
- Troubleshooting information to resolve instrument problems
- Tools to independently validate the instrument, sampling techniques and methods
- Templates and test limits for testing standards including certified standards (such as those traceable to independent laboratories such as NIST or NPL), manufacturer-specified standards or user-defined standards
- Templates for recommended qualification standard operating procedures (SOPs)
- Historical validation reports with audit trails.

When purchased with ValPro, instruments are shipped with their original manufacturing test data, along with complete validation documentation. They are installed by trained or certified service engineers who provide complete Installation Qualification (IQ) and ensure each instrument meets or exceeds all qualification performance test parameters.

Chapter 2 Regulatory Requirements

Regulatory requirements play a major role in all qualification and validation issues. ValPro is designed to assist users with meeting regulatory requirements and guidelines. It was developed specifically to satisfy the following validation requirements:

- cGMP (Current Good Manufacturing Practices) requirements defined in the Code of Federal Regulations (21 CFR), Parts 210 and 211, which govern activities of pharmaceutical manufacturers regulated by the United States Food and Drug Administration (FDA)
- cGMP requirements defined in 21 CFR, Part 820 (*Quality System Regulation*), which governs manufacturers' production and process controls for automatic, mechanical and electronic equipment (Subpart G), and servicing (Subpart N)
- cGMP requirements defined in 21 CFR, Part 11 (Electronic Records, Electronic Signatures, Final Rule). See the "Quality Documents" section of this manual for a detailed explanation of the Madison, Wisconsin site's compliance with these guidelines
- ISO 9001:2000 guidelines established by the International Standards Organization (ISO)
- Additional agency-specified validation requirements or pharmacopeial-recommended methods appropriate to the industry, instrument type and purpose.

Chapter 3 Validation Overview

Validation is a comprehensive process that provides documented evidence that systems perform as expected and required. It enables answers to these basic questions:

- How do I know the system is working properly?
- Can I trust the data generated by the system?

Validation is a process of ensuring that a system, which includes the instrument, method, and procedures, is fit for a specific process or application. It is a FDA requirement for the pharmaceutical industry, and is the user's responsibility to assure compliance with this requirement.

A validation program consists of pre-defined activities that are conducted according to procedures and test cases. The validation activities are typically defined in a master validation plan established by the end user, which documents the policy, philosophy, strategy, and methodology for validating the system. The validation program also includes a validation protocol, which is a written plan that states how validation will be conducted. It includes test parameters, acceptance criteria, product characteristics, production equipment, and decision points on what constitutes acceptable results.

Thermo Electron Corporation is committed to supporting the validation efforts of its customers.

Method validation

Method validation is a fundamental component of any validation program. It is performed by users to verify that an analytical procedure defined for a particular test is suitable for its intended use. It uses samples or standards of known concentration or value that are similar to the unknown samples tested during routine analysis. The outcome of method validation is typically used to evaluate the quality, reliability and consistency of analytical results. Satisfactory method validation results can be obtained only with equipment that is performing properly.

Methods should be validated before they are put into routine use. Method validation should also be performed whenever the scope of the method has changed or the conditions in which a method was previously validated have changed. Published guidelines covering method validation include the United States Pharmacopeia (USP) General Chapter <1226> "Validation of Compendial Methods," the U.S. Food and Drug Administration (FDA) Draft Guidance for Industry: Analytical Procedures and Methods Validation, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Industry: Text on Analytical Procedures (ICH Q2A) and Validation of Analytical Procedures (ICH Q2B).

ValPro provides testing templates that can be easily modified to develop and perform user-defined method verification tests. This enables method verification tests to be incorporated into the ValPro validation testing suite. Thermo Electron Corporation also has trained specialists available to provide fee-based assistance its customers in developing valid methods, further helping to ensure regulatory compliance.

Software validation

Software validation confirms that a software product performs as specified and meets a user's testing needs. It is a process in which both the vendor and customer participate.

Vendor role

The quality procedures, as documented here, are those implemented and followed at the Madison, Wisconsin development and manufacturing site. Thermo Electron Corporation software is validated to guarantee that it performs accurately and as specified. It is designed and tested according to stringent cGMP and ISO 9001:2000 certified procedures. The procedures are part of the site's Product Development Process (PDP) which defines the lifecycle of products and their adherence to the site's quality guidelines. The software's marketing specification, design, test plans and test results are thoroughly documented and archived in the project's Design History File (DHF), as prescribed in the FDA's Quality System Regulations (QSR).

The "Design Qualification (DQ)" section of this manual describes the PDP and details how software developed at the Madison, Wisconsin site is designed and tested.

Customer role

The customer's part in software validation is to evaluate the product and qualify it as meeting the customer's specified needs. This includes qualifying the vendor to verify that its product is compliant with the industry and regulatory standards. It also includes defining the tasks for which the software will be used, along with the system and environment in which it will operate. These criteria are then evaluated against the software to determine the software's suitability.

The Design Qualification (DQ) section of the ValPro System Qualification manual provides information to assist customers with software validation.

Chapter 4 System Qualification

System qualification is a process of ensuring that a system's specification is appropriate for its intended use and that the system performs according to that specification. It is the responsibility of the supplier and customer.

System qualification is a key component of an instrument user's validation plan. It is an ongoing process in which an instrument and its software are tested to provide evidence that they are performing properly and as intended. System qualification comprises the following components to verify the design, installation and use of the system:

- Design Qualification (DQ)
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ).

ValPro assists users of the Thermo Electron Corporation instruments and software to perform system qualification.

Design Qualification (DQ)

Design Qualification (DQ) analyzes how the manufacturer develops, manufactures, tests, releases and supports the product. In the case of a software product, DQ focuses on the software development process to ensure that similar guidelines are followed.

Specific activities that take place during DQ include:

- Determining critical features and specifications
- Determining the capabilities of the instrument
- Comparing the environmental needs of the instrument
- Choosing an instrument that gives the best features and specifications match, and that is most suitable for the customer's intended use.

Together, these elements help the buyer ensure that the instrument to be purchased is appropriate for its intended use and suitable for installation in its intended environment.

The Design Qualification (DQ) section of the *ValPro System Qualification* manual provides information instrument buyers can review to verify that that the design of the instrument and software products are sound and comply with industry standards.

The DQ material includes descriptions of:

- Product development procedures
- Product quality procedures
- Company organization charts
- Product specifications
- Environmental specifications.

Typically, the verification and review of this material is sufficient to qualify the design process and procedures.

Installation Qualification (IQ)

Installation Qualification (IQ) is performed by a trained and certified Thermo Electron service engineer when an instrument is installed in the buyer's environment. It verifies and documents that the equipment has been delivered as ordered and specified in the DQ, that it is defect and damage free, and that it has been properly installed.

The FDA views IQ as establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. Thermo Electron Corporation believes that to be compliant with this definition, IQ of its products should include testing to verify that performance meets or exceeds manufacturing specifications.

Specific activities that take place during IQ include:

- Confirmation of pre-installation requirements, as defined in the instrument documentation, such as your *Site and Safety Information* manual
- Unpacking and inspection of system components
- Checking and confirming customer understanding of system safety precautions
- Setting up the instrument
- Setting up the computer and printer
- Verifying the operation of the instrument, computer and printer
- Connecting the system components
- Verifying component installation and operation
- Installing the ValPro and analysis software on computers not supplied by Thermo Electron Corporation
- Verifying software installation
- Running the ValPro qualification tests for the instrument
- Confirming that the instrument performance meets or exceeds defined manufacturing specifications
- Training the customer on the operation and use of the system and software

- Completing the installation certificate, certification label and other IQ paperwork
- Verifying that the system passes initial operational test requirements
- Preparing the service log (electronic or hard-copy version).

Thermo Electron recommends that IQ be performed when:

- A new instrument is installed
- There is a major change to the system (beyond, for example, installation of user-replaceable parts)
- An instrument has been moved:
  - To a new room (environment change)
  - In the same room but to a different power source.

ValPro provides detailed installation procedures and reports, tracking histories and certification documentation to ensure that all systems are installed in accordance with IQ specifications. In addition, ValPro provides a detailed explanation of the instrument tests used during IQ.

A key component of IQ is running the ValPro qualification tests to verify that the instrument is performing within manufacturing specifications once the instrument is installed. The ValPro tests utilize traceable standards. The standards are used to run performance tests which include pharamacopeial-recommended tests to verify instrument accuracy and to verify the performance of the instrument against manufacturing specifications.

Upon successful completion of IQ, the service engineer provides users with detailed ValPro system qualification software training, illustrating the ValPro tools that can be utilized for Operational Qualification (OQ) and Performance Qualification (PQ). The service engineer also attaches a certification label to the instrument and provides the user with a Thermo Electron Corporation installation certificate. The IQ procedure form is signed and approved by the customer.

Operational Qualification (OQ)

Operational Qualification (OQ) is a check of the instrument's basic operation that is done to demonstrate that the instrument performs consistently and as specified by its manufacturer and as intended by the user for daily use. OQ tests critical areas such as data collection against factory specifications to prove that subsequent analytical measurements are accurate, precise and reproducible.

With ValPro's internal traceable standards, system tests for performance, resolution, and software algorithm accuracy can be performed. ValPro also incorporates recommended pharmacopeial tests appropriate to the instrument.

ValPro can also be set up to include the user's own standards in OQ testing. Virtually any standard can be incorporated into ValPro for OQ testing, including:

- Primary standards, which are certified by nationally or internationally recognized institutions, such as NIST (National Institute of Standards and Technology), NPL (National Physical Laboratory) and ASTM (American Society for Testing and Materials).
- Secondary standards, which are traceable back to primary standards or otherwise verified, for example, through an independent test method with a certificate from the manufacturer.
- User-prepared standards that are traceable to primary or secondary standards, or are otherwise verified to an independent test method.

Trained personnel perform OQ at a frequency specified by the instrument user, typically daily or weekly.

For OQ, ValPro also provides detailed qualification reports, qualification histories and complete troubleshooting information. For third party verification, Thermo Electron offers semi-annual and annual re-certification services to ensure continuous qualification compliance.

Performance Qualification (PQ)

Performance Qualification (PQ) is a testing regimen established by an instrument user. It confirms the operation and accuracy of the instrument for its intended use. Typically, the user's standard operating procedures specify the PQ tests, how often they are performed and by whom, and how the results are reported and saved.

ValPro provides the flexibility needed to accommodate any PQ requirement. It allows independent qualification of the instrument and any qualitative or quantitative methods used. This, coupled with a selection of customizable testing templates (workflows), allows virtually any standard to be incorporated into ValPro for PQ testing.

In addition, Thermo Electron offers fee-based services to help customers develop customized PQ testing.

Chapter 5 General Company Information

This section provides general information about Thermo Electron and its approach to product development and quality.

Corporate headquarters

Thermo Electron Corporation has its headquarters at the following location:

Thermo Electron Corporation
81 Wyman Street, P.O. Box 9046
Waltham, MA 02454-9046

Telephone: (781)-622-1000
Fax: (781)-622-1207

Manufacturing and development location

Thermo Electron Corporation's ISO 9001:2000-certified development and manufacturing center is based at the following location:

Thermo Electron Corporation
5225 Verona Road
Madison, WI 53711

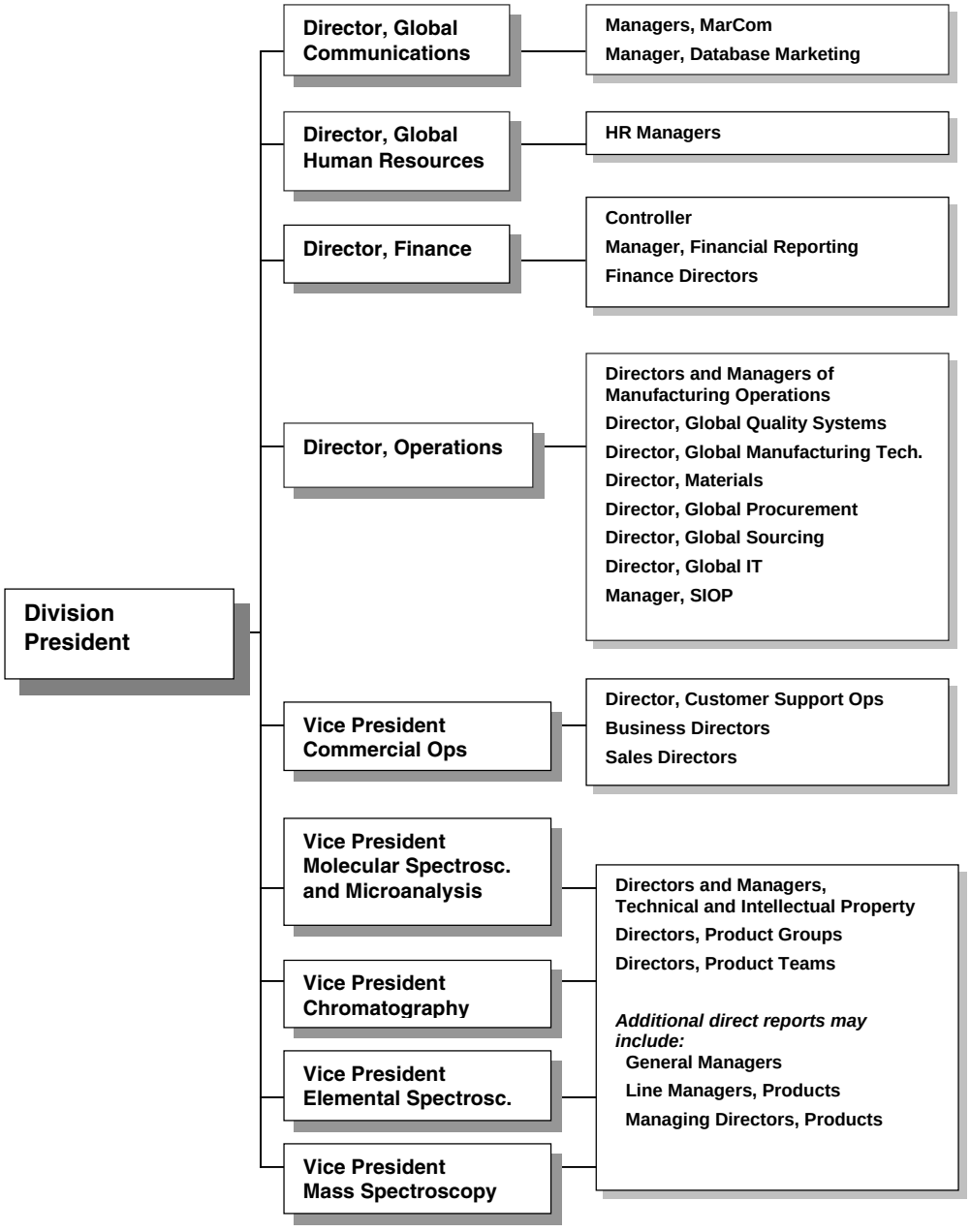
Telephone: (608) 276-6373
Fax: (608) 273-6883
E-mail: techsupport.analyze@thermo.com

An organization chart of the Thermo Electron Corporation Madison, Wisconsin development and manufacturing site appears on the following page.

You can find more information about Thermo Electron Corporation on the Internet at www.thermo.com.

Organization chart

This is the organization structure for Thermo Electron's Scientific Instruments Division, which includes the Madison, Wisconsin development and manufacturing site:



Primary business focus

Thermo Electron Corporation, incorporated in 1956, develops and manufactures instruments, scientific equipment, and integrated software solutions for laboratory and industrial applications sold worldwide. The Company's businesses are managed in three segments: Measurement and Control, Spectra-Physics (Optical Technologies), and Life and Laboratory Sciences.

The Measurement and Control businesses provide nearly every industry with analytical, quality assurance/quality control, and process-control tools. Products include analytical tools, online process instruments, precision temperature-control systems and a comprehensive range of chemical, radiation and explosives-detection instruments.

The Spectra-Physics group provides a wide range of lasers and photonic-related products and services. Our lasers and photonics capabilities are used in a variety of applications and industries, including scientific and medical instruments, computer and microelectronics manufacturing, image recording and graphics, industrial manufacturing, and research.

The Life and Laboratory Sciences group provides advanced analytical technologies, scientific equipment, and laboratory consumables used in research and development, diagnosis, and quality assurance. Products are used in applications that serve the pharmaceutical, healthcare, biotechnology and other research and industrial laboratory markets.

Life and Laboratory Sciences group

Thermo Electron Corporation's Life and Laboratory Sciences group is organized as four divisions: Bioscience Technologies, Informatics and Services, Clinical Diagnostics, and Scientific Instruments

Bioscience Technologies division encompasses instruments and consumables such as microplate-based handling and reading equipment; optical biosensors, thermal cyclers, DNA purification systems, SNP scoring systems, capillary electrophoresis (CE), laboratory automation, software and instruments, reagents, microtiter plates, and liquid-handling pipettes.

Informatics and Services division offers laboratory information management systems (LIMS), chromatography data systems, analytical data archival and instrument integration solutions to customers in regulated and nonregulated industries such as pharmaceuticals, biotechnology, petrochemicals, chemicals and food and beverage.

Clinical Diagnostics division provides equipment and supplies used by healthcare laboratories in doctors' offices and hospitals to detect and diagnose diseases. Products in this group include sample-preparation instruments and materials to highlight abnormal cells, blood gas and ion-selective electrolyte (ISE) consumables, chemistry reagents, clinical-biochemistry instruments and automation equipment and rapid diagnostic tests for use in health care settings.

Scientific Instruments division, including the Madison, WI site, provides advanced analytical and spectroscopy instruments and software to customers in regulated and nonregulated production and research industries such as pharmaceuticals, biotechnology, petrochemicals, chemicals and food and beverage.

Thermo's advanced analytical instruments include spectroscopy instruments, mass spectrometers, liquid chromatographs, gas chromatographs, multi-instrument combinations of these technologies, and affiliated software, along with the vials, syringes, and columns necessary for chromatography. These products are used by the pharmaceutical industry for drug development, testing, and quality control, and by the biotechnology industry for research.

Spectroscopy instrumentation is used for molecular and elemental analysis based upon energy and light measurements. Thermo instruments include atomic absorption, inductively coupled plasma, inductively coupled plasma-mass spectrometers, Fourier transform infrared (FT-IR), near-infrared (FT-NIR), Optical Emission, Raman, ultraviolet/visible (UV/Vis), fluorescence, X-ray diffractometry and X-ray fluorescence instruments, as well as microscopes, sampling accessories, software and spectral reference databases. Customers include pharmaceutical, specialty chemical, and basic material producers, who use these instruments either in a laboratory or integrated into the production process.

Thermo Electron Corporation products provide rugged, reliable and expandable instrument platforms for dedicated sampling in an industrial environment. They include easy-to-use, intuitive quality control/quality assurance analysis software and may include complete chemometric support provided through software such as TQ Analyst. Products are designed to help customers comply with stringent validation guidelines set by the United States Pharmacopeia (USP) and the Food and Drug Administration (FDA).

Financial information

Current financial information about the company is available on the Internet at www.thermo.com.

Quality management

Thermo Electron's, Madison, Wisconsin site is certified by KEMA-Registered Quality, Inc. to ISO 9001:2000 standards and has a compliant quality system in place.

The quality system at the site is defined by four levels of documentation to meet the requirements of ISO 9001 and to ensure adequate control. Documentation includes the Corporate Quality Manual and supporting quality procedures, work instructions, and records and forms. The quality system provides a structured approach to actively seek out and implement improvements in the quality of products, processes and services on an ongoing basis.

Top management at the Madison, Wisconsin site is responsible for the development, implementation, and improvement of the corporate quality system. The quality policy and objectives for quality embody the company's commitment to meeting customer needs, statutory and regulatory requirements. Specific, measurable quality objectives are developed annually.

Quality policy

The Madison, Wisconsin site's quality policy and objectives for quality are displayed openly as a sign of our pride and commitment and as a clear reminder of our focus and direction. Our quality policy states:

> *The delivery of Thermo Electron Corporation products and services that consistently meet and exceed customer expectations is our quality focus and customer service goal. We will ensure that all Thermo Electron Corporation, Madison site employees strive to improve the processes that affect customer satisfaction and understand that our customers are who we serve and depend upon for our company's continued financial success.*

Quality organization

Thermo Electron Corporation quality organizational structure illustrates the responsibilities and authorities of personnel who manage, perform and verify work affecting the quality of products and services.

The division president is the leader of the quality efforts and is responsible for the delegation of the responsibilities for quality and for the efficient operation of the company.

Vice presidents and directors are responsible for the operation of the functions reporting to them. These responsibilities include both daily operations and strategic and tactical planning. They ensure that the quality policies operate effectively in their functions.

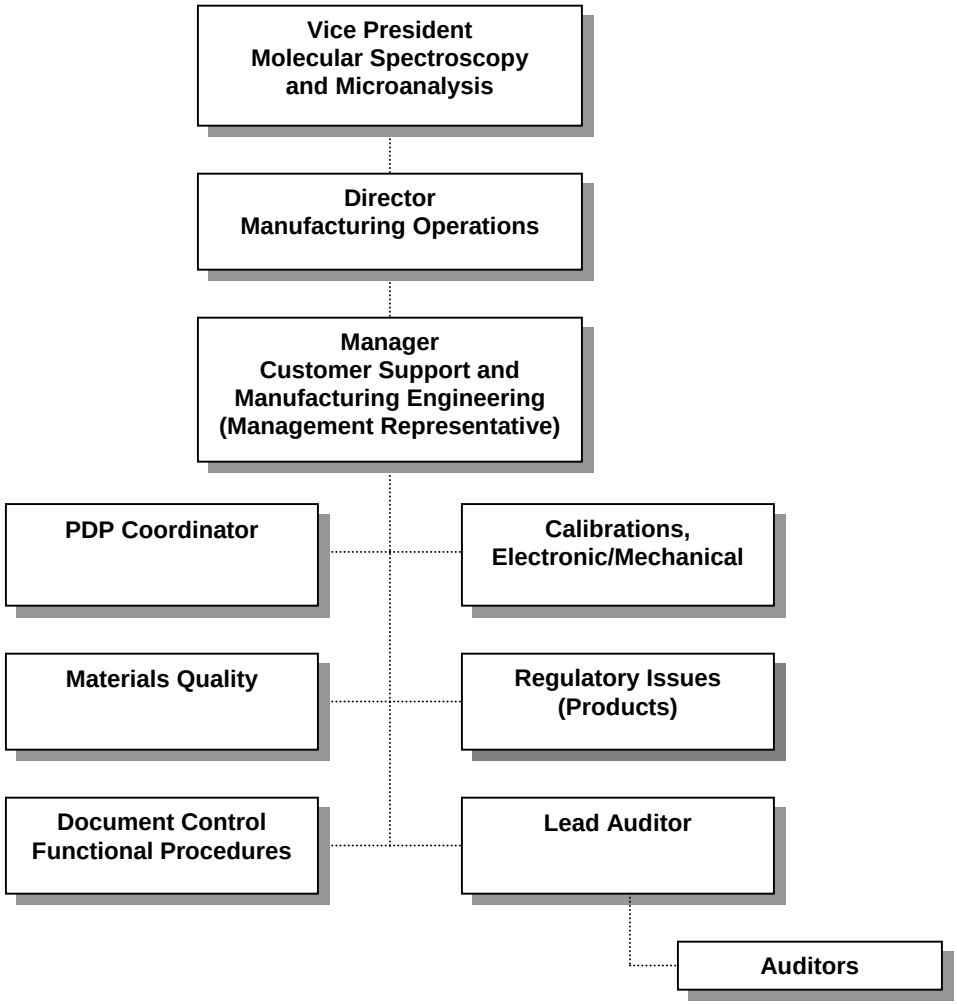
Product and team managers and supervisors ensure that the quality policies are being carried out on a daily basis. They may delegate authority for implementing the quality functions within their departments, but they are responsible for its function.

Quality is the responsibility of each employee of Thermo Electron Corporation. Their responsibilities for activities affecting quality are specified explicitly in the quality manual, procedures, and work instructions. In addition, each employee has sufficient authority to identify, document and communicate any issues related to the quality management processes and their effectiveness.

Audits of the quality system are carried out by trained auditors, who are independent of the functional area being audited, according to internal quality system procedures.

Quality matrix

This chart shows the quality organization structure in place at Thermo Electron Corporation's Madison, Wisconsin development and manufacturing site:



Chapter 6 Design Qualification Overview

This chapter gives a summary of information covered in the supplier assessment part of Design Qualification (DQ). Additional more detailed information is in the *ValPro System Qualification* manual.

Certified quality system

Thermo Electron Corporation's Madison, Wisconsin development and manufacturing site (certified as Thermo Electron Scientific Instruments Corporation) is certified by KEMA-Registered Quality, Inc. to ISO 9001:2000 standards and has a compliant quality system in place. ISO 9001 is a quality system model for quality assurance in design, development, production, installation and servicing.

The quality system for the site is described in a procedure document titled Corporate Quality Manual and is followed in every project undertaken at the site. At the end of each project, a quality review is held to evaluate the project's adherence to the quality system. The site also undergoes regular ISO 9001 audits and internal audits of its adherence to the quality system.

Software product compliance

The Madison, Wisconsin site's software development procedures adhere to ISO 9000-3 (*Guidelines for the Application of ISO 9001 to the Development, Supply and Maintenance of Software*) as part of its ISO 9001 certification.

Product lifecycle

All hardware and software products are developed, verified and validated according to procedures defined in the site's Corporate Quality Manual and Product Development Process (PDP). The PDP and associated quality procedures define the product development lifecycle.

Declaration of conformity

The Madison, Wisconsin site provides a declaration of conformity for each of its products. This document states compliance to applicable European Union New Approach Directives. See the Quality Documents section for a copy of the declaration of conformity for your instrument.

Availability of records to regulatory agencies

All project records and pertinent project documentation are archived in the design history file (DHF), as prescribed in the U.S. Food and Drug Administration's Quality System Regulations (QSR), documented in 21 CFR Part 820. The DHF provides a compilation of records describing the design history of a finished product. The DHF covers the design activities used to develop the device, accessories, major components, labeling, packaging and production process. The items in the DHF are easily retrievable and are accessible to regulatory agencies as needed.

Customer feedback and response

Thermo Electron Corporation provides a product hotline for domestic (U.S.A.) customers to give feedback relating to product quality issues. To provide feedback, customers can send an e-mail message via the corporate web site at www.thermo.com or to techsupport.analyze@thermo.com. They can also use the Software Action Request Form and the System Action Request Form provided in the Master Forms section of this manual. Messages are forwarded to Thermo Electron Corporation's technical support staff where they are assigned to the appropriate person for resolution.

For domestic (U.S.A.) customers, telephone technical support for Thermo Electron Corporation products is available. It is included at no charge during the warranty period and is included as a benefit with the purchase of a service contract. Technical support personnel specifically trained in the operation of Thermo Electron Corporation products provide support for these calls.

International customers (those who purchase their instrument outside the U.S.A.) contact their local Thermo Electron sales or service representative for available product support.

Change control system

Products developed and manufactured at the Madison, Wisconsin site are controlled by the Change Control Notice (CCN) procedure. CCNs assure proper approval for all product changes. They also trigger the release of technical bulletins, which are issued to Thermo Electron Corporation field representatives to keep them up to date on pertinent changes.

Product Development Process (PDP)

The Madison, Wisconsin site's Product Development Process (PDP) is a management tool used to guide an idea through the necessary steps to produce a new, quality product. The project team is responsible for determining the specific development steps that will best meet the project goals.

Design and development planning

Each phase covered by the PDP has specific plans listed as deliverables. Design and development activities are assigned to a qualified project manager who is equipped with adequate resources. As the design evolves, specified plans are updated as needed.

Team meetings are held regularly with quality records developed to communicate issues to all involved. A project file is maintained for ongoing reference by design team members.

Phased design and development approach

The five development phases of the PDP are:

- Project Approval Phase
- Discovery Phase
- Concept Phase
- Design Phase
- Launch Phase.

Design and development traceability

The site's PDP requires documented traceability from product specification to design specification to test plan to test results and acceptance criteria. The traceability matrix, developed during the Concept Phase, provides development lifecycle traceability.

PDP activities and deliverables

Major projects, such as hardware or software development projects, use the full PDP lifecycle. The activities and deliverables described in each phase are designed to initiate the necessary actions. They also apply certain checks and balances in order to maximize the chances for market acceptance and provide an acceptable return on investment.

The project phase procedures generally list major activities in sequential order, yet phase overlap is both expected and, in most cases, necessary to achieve time-to-market goals.

The deliverables required from a particular project depend on the project scope and the nature of the project. Before a project phase begins, the project team reviews the PDP checklist, notes those deliverables required by the PDP and agrees on other deliverables to be developed for that phase so that the expectations are clear. These deliverables are recorded on the PDP checklist. An approval form and Portfolio Management Team (PMT) review is required for each phase. The PMT is the highest-ranking management team charged with managing the product portfolio matrix and pipeline.

Project Approval Phase

Project Approval is the first phase of the product development process, during which an idea for a new project is formulated, discussed, documented and approved to enter the Discovery Phase. These activities are directed by the product manager.

An initial project manager works with the marketing staff to develop an estimated return on investment (ROI) for the project. The required project approval form describes the product, the reasons to pursue the product and how the new product fits in with company strategy. The document also includes requested resources, Discovery Phase completion date estimate and the preliminary project and product managers.

Discovery Phase

The Discovery Phase evaluates the potential of a new product idea and is directed by the product manager. The project manager reviews the marketing documents and compiles a concept phase schedule, budget and a listing of requested resources.

The product manager, with the project manager and team members, reviews required deliverables and determines which additional deliverables are appropriate for the project. Deliverables for the Discovery Phase include such items as the preliminary business plan, and schedule, budget, and resources for the Concept Phase.

Discovery Phase Review and Approval

When the activities leading up to the Discovery Phase review are complete, the review is held. The documents are reviewed and updated according to the Marketing review team decisions. PMT approval is required to move the project forward to the Concept Phase.

Concept Phase

The Concept Phase defines the critical product, project and process elements and is directed by the product manager or project manager, with key participation by the project team. The key activities in the Concept Phase include minimizing risk in the Design Phase schedule and completing the traceability matrix. The traceability matrix details the product design specifications along with test plans.

The product manager, with the project manager and team members, reviews deliverables required for the specific type of project and determines which additional deliverables are appropriate for the project. Deliverables typically prepared for the Concept Phase include components of the project plan and traceability matrix, project plan and budget, business plan, manufacturing and support plans. Additional deliverables may be required.

Concept Phase Review and Approval

At the end of the Concept Phase (before the Design Phase begins), there is a technical review of the project. The main purpose of this review is to have a comprehensive examination of the project plan conducted by a cross functional team to identify potential problems, technical risks and oversights before they have a negative impact on the project/product. The result of the review will either be a recommendation that the project is ready to proceed to the Design Phase from a technical point of view, or a list of outstanding issues to be addressed by the project team. If issues are found, further review is required before the project moves forward. PMT review and approval is required to move the project forward to the Design Phase.

Design Phase

This phase provides the information required to define, build, debug, verify, and validate the product in accordance with the product specification. The phase is directed by the project manager, with key participation by the project team.

The project manager, with the team members, reviews deliverables required for the specific project and determines which additional deliverables are appropriate for the project. Deliverables for the Design Phase include prototypes and pilot builds, test plans, user documentation, and the product configuration guide. Additional deliverables may be required.

Design Phase Review and Approvals

Several key reviews and approvals are required during the Design Phase. A verification test plan review assures that the plan is complete and comprehensive, and a review of the verification test results ensures that the results conform to the performance specification. Results of these reviews are documented in the design history file (DHF). A validation test plan review is also performed during the Design Phase.

Launch Phase

This phase prepares the product for full release to the marketplace, introduces the product to the sales force and offers it for sale to the customer. The phase is directed by the product manager or project manager, with key participation by the project team, the sales, marketing, manufacturing and customer support groups, and external customers.

The deliverables and activities to be considered for the launch phase include the product introduction plan, software release candidate, user documentation, service documentation and training plans. Additional deliverables may be required.

PDP Quality Audit

A PDP quality audit is required to ensure that all products meet internal quality standards, and to ensure the integrity of all manufacturing processes. Any non-compliance issues from the quality audit must be resolved prior to the first shipment to a customer.

Launch Phase Review and Approval

Prior to product launch, PMT approval of the product sales proposal is required. During the launch phase, a review of the validation test results ensures that the results conform to product requirements.

Post-Launch activities

Once a product has been launched, a number of activities take place to optimize the market opportunity for the product within the site's guidelines for quality, customer satisfaction and return on investment.

Design and development review

Reviews and approvals are specified in the Product Development Process and the traceability matrix at each phase of the project in order to move to the next phase. The result of the review will either be a recommendation that the project is ready to proceed from a technical point of view or a list of outstanding issues to be addressed by the project team. If issues are found, further review is required before the project moves forward. PMT review and approval is required to move the project forward to the next phase.

Design and development testing

Testing required for each design and development project is based on internal quality procedures and documented in the project documents.

Design verification

Design verification is performed to ensure that product specifications have been fulfilled and that the product operates as designed. This includes failure analysis of key components, system integration, assembly and test of both an engineering prototype and an alpha prototype. Design output is verified by building the product according to the design and testing it to see if it functions as intended.

Design validation

Design validation is the process of determining that the end result matches the initial concept. Validation confirms by examination and objective evidence that the product specifications for specific intended end use can be consistently fulfilled. The purpose of this is to show that the product specifications fulfill the user's needs for its specific intended end use. Results are collected and reviewed from validation tests on products that are as close as possible to the released product, have been performed under normal operating conditions, and have been carried out redundantly.

Chapter 7 ValPro Qualification Tests

ValPro includes a comprehensive set of pharmacopeial-recommended qualification tests to verify instrument performance.

The tests are automated and require the presence of the ValPro traceable, internal standards. Acceptance limits are based on Thermo Electron's manufacturing specifications and ASTM, USP, EP, or JP requirements, as appropriate for the instrument and expected use. The tests are performed during the manufacturing process to verify instrument performance.

The ValPro tests are run as part of IQ to verify that the newly-installed instrument is performing according to factory specifications. Thereafter, they are run regularly as part of OQ to verify instrument performance over time.

Antaris near-IR tests

This section describes each of the ValPro qualification tests for Antaris near-infrared (NIR) instruments. Detailed information about the test parameters is included with the ValPro documentation.

Energy ratio test

This test detects changes in energy distribution in the single beam spectrum. It is used to verify the performance of the source, as well as alignment of the instrument and optical integrity, over time.

Failures in this test can indicate the interferometer is misaligned, the source has failed, or that optical components have degraded or are misaligned.

System optical resolution test

This test collects a spectrum using the water vapor peak at 7,299 cm^{-1}. The expected resolution result is specified to be between 1.6 cm^{-1} and 2.2 cm^{-1}.

Failures in this test can indicate a source failure or that there are electronic problems.

Noise level test

This test measures the instrument's noise level for transmission analysis. It collects open beam spectrum and calculates the signal-to-noise in the spectral range from 6,800 cm^{-1} to 5,800 cm^{-1}. Noise can be caused by:

- System out of alignment.
- Beam path not configured correctly.
- Faulty detector.
- Faulty electronics.
- Faulty power supply.

Increased noise levels can affect both qualitative and quantitative analysis results. Many experts consider excessive noise to be the single most likely cause of failure of an analytical method.

Short-term stability test

This test compares the results of five identical consecutive background and sample scans to determine the short-term stability of the instrument. It verifies that the variance between each of the background and sample scan sets is within specified limits.

Failures in this test can indicate that the beamsplitter is misaligned, the OBC board is faulty or the power supply is faulty.

USP wavelength accuracy test

This test measures the frequency (or wavelength) accuracy of the instrument at specific wavenumber positions. It uses the polystyrene standard in the ValPro validation wheel.

USP refers to this as wavelength uncertainty.

Failures in this test can indicate that the electronics are faulty, the laser is faulty, or the aperture is set incorrectly.

Method transferability test

This test verifies the transferability of the instrument by predicting the thickness of the polystyrene sample included in the ValPro validation wheel.

USP photometric linearity test

This test verifies the photometric scale of the instrument using the validation wheel's transmission standards. The photometric scale is measured as the slope of the line between the measured absorbance and the absorbance rating of the transmission standards.

Failures in this test can indicate a faulty or mis-adjusted detector.

Note ValPro also provides a USP Photometric Linearity Test for reflection standards that can be purchased separately.

Antaris IGS mid-IR tests

This section describes each of the ValPro qualification tests for Antaris IGS mid-infrared (MIR) instruments. Detailed information about the test parameters is included with the ValPro documentation.

The tests were designed to satisfy the qualification tests of both the European Pharmacopoeia (EP), Fourth Edition, General Chapter 2.2.24, and the Japanese Pharmacopoeia (JP), Fourteenth Edition, Part I, General Tests, Process and Apparatus, 23. Infrared Spectrophotometry, Instrument and adjustment. Additional useful qualification tests were identified by Thermo Electron to supplement the EP and JP requirements. Some of the additional tests are based on ASTM E1421-99.

Energy ratio test

This test detects changes in energy distribution in the single beam spectrum. It is used to verify the performance of the source, as well as alignment of the instrument and optical integrity, over time. This test is based on ASTM E1421-99, Level One test for energy ratio.

Failures in this test can indicate the interferometer is misaligned, the source has failed, the beam is obstructed, or that optical components have degraded or are misaligned.

Noise level test

This test measures the instrument's noise level for transmission analysis. It collects an open beam spectrum, calculates the signal-to-noise, and reports the noise level. This test is based on ASTM E1421-99 Level One test for noise level.

Increased noise levels can affect both qualitative and quantitative analysis results. Many experts consider excessive noise to be the single most likely cause of failure of an analytical method. Noise can be caused by a misaligned system, a faulty detector, faulty electronics, or a faulty power supply.

Wavenumber accuracy test (EP)

This test measures the frequency (or wavenumber) accuracy of the instrument at specific wavenumber positions. It uses the traceable 1.5 mil polystyrene standard in the ValPro validation wheel. This test is defined in the European Pharmacopoeia (EP).

Failures in this test can indicate that the instrument's electronics are faulty, the laser is faulty, the optics are misaligned, or the aperture is set incorrectly.

System optical resolution test (EP, JP)

This test verifies the resolution of the Antaris IGS system by measuring the minimum and maximum heights of two polystyrene peaks. It uses the traceable 1.5 mil polystyrene standard in the validation wheel. This test is defined in the Japanese Pharmacopoeia (JP) and the European Pharmacopoeia (EP).

Failures in this test can indicate a source failure or that there are electronic problems.

Wavenumber repeatability (JP)

This test verifies that wavenumber measurements are repeatable. Using the traceable 1.5 mil polystyrene standard in the validation wheel, two spectra on the same sample are compared for peak location. This test is defined in the Japanese Pharmacopoeia (JP).

Failures in wavenumber variance can indicate that the instrument's electronics are faulty, the laser is faulty, the optics are misalignment, or the aperture is set incorrectly.

Intensity repeatability (JP)

This test verifies that intensity measurements are repeatable. Using the traceable 1.5 mil polystyrene standard in the validation wheel, two spectra on the same sample are compared for peak location and intensity. This test is defined in the Japanese Pharmacopoeia (JP).

Failures in intensity variance can indicate that the beam is blocked or that the screen is malfunctioning.

Photometric linearity (transmission)

This test verifies the photometric scale of the instrument using the validation wheel's NPL-traceable NG11 glass transmission standard. The photometric scale is measured as the slope and intercept of the line between the measured % transmittance and the % transmittance rating of the transmission standard.

The certificate for each validation wheel provides the traceable %T values for the NG11 glass standard.

Note Linearity is not tested for MCT detectors.

Short-term stability test

This test compares the results of five consecutive sample scans to determine the short-term stability of the instrument. It verifies that the variance between the sample scans is within specified limits.

Failures in this test can indicate a faulty source, interferometer misalignment, problems with the detector or electronics, or optical (non-interferometer) misalignments.

Software algorithm qualification test

This test verifies the accuracy of software algorithms used in the system. It tests various algorithms to ensure they generate the expected result each time they are run throughout the software life.

The test measures a polystyrene spectrum using a variety of analytical methods, including:

- The Classical Least Squares (CLS) algorithm
- The Distance Match (DM) algorithm
- Measuring the area beneath the curve
- Beers Law
- Stepwise Multiple Linear Regression (SMLR)
- QC Compare Search
- Partial Least Squares.

Running the ValPro qualification tests

The ValPro qualification tests are run from the Thermo Electron software simply by selecting the qualification tests from the menu or by clicking a button on the main screen's toolbar.

The tests, with the appropriate options selected in the ValPro Options dialog box, include:

- The standard set of ValPro tests using the traceable internal standards
- The algorithm qualification test
- Specific sampling module tests (if appropriate to the instrument)
- User-defined qualification tests.

Qualification test troubleshooting

The *ValPro System Qualification* manual includes troubleshooting information to help users resolve problems that might occur when running the ValPro qualification tests.

Chapter 8 Support Overview

Customer satisfaction and support are key components of the Madison, Wisconsin development and manufacturing site's quality system and Product Development Process. The main elements of the support program are outlined in the following sections. (For up-to-date information on support products, refer to the Thermo Electron Corporation web site, www.thermo.com.)

Qualification services

Fee-based qualification services require the purchase of ValPro and include the following offerings:

- Installation Qualification
- System qualification (a pharmaceutical industry requirement recommended annually)
- Qualification assistance after system moves.

Warranty

Systems purchased domestically come with a standard warranty that is in effect for twelve months from the date of installation. The international system warranty is fourteen months from the date of shipment or twelve months from the date of installation (whichever is earlier). The warranty includes:

- Labor, parts and travel
- On-site installation
- On-site maintenance and repair
- Technical support.

Method development

Thermo Electron Corporation offers the following method development support options for purchase separately or in combination. Options include:

- Feasibility assessments (available for some product lines)
- Sampling solution support
- Experimental design support
- Chemometric modeling support
- Method review
- Method validation
- Method transfer and implementation
- Method maintenance
- Custom method development.

Support and service plans

Instruments include a standard on-site maintenance and repair contract under warranty.

Several maintenance and support plans are available to customers of Thermo Electron Corporation products. They include options such as preventive maintenance, factory-certified replacement parts, software service packs, priority technical support, accelerated on-site response, and online knowledge base. There are a variety of plans available depending on the level of service desired.

Help desk

Telephone technical support is available through Thermo Electron Corporation's help desk at no charge to all domestic (U.S.A.) customers of Thermo Electron products while under warranty or a service contract. Internal quality procedures define the activities required to respond to product support calls, customer requests and complaints.

Support for international customers (outside the U.S.A.) is provided through their local Thermo Electron sales or service representative.

Customer training

Training of key customer personnel is an essential part of system validation. Thermo Electron Corporation offers a wide range of training options. A complete course catalog, providing specific course listings and descriptions along with the current course calendar, is available on the Thermo Electron Corporation web site, www.thermo.com. Customized training is also available.

Classes in North America are offered at Thermo Electron Corporation's development and manufacturing site in Madison, Wisconsin. They are also available at satellite sites throughout the world and at customer facilities.

Web site

As a resource to its customers, Thermo Electron Corporation provides a web site dedicated to its products. The web site includes product information, application solutions and technical support. The contents of the technical support area include:

- Information on educational and consulting services
- Information on support programs and services
- System qualification information
- Technical support contact information
- Thermo Electron Corporation's newsletters.

The address of the web site is www.thermo.com.

Chapter 9 Product Development Glossary

This section provides a selection of glossary terms used by the Madison, Wisconsin development and manufacturing site in the Product Development Process (PDP) and its related product design and development procedures.

acceptance criteria – The definition of the objective evidence that the correct result was obtained during testing. A test may have multiple acceptance criteria for various steps in the test procedure. Examples of acceptance criteria are screen shots, comparisons to references, and measured values obtained from the product during testing.

alpha build, hardware – A largely integrated, functioning system(s) with respect to the functional specifications and engineering performance specifications. Some features may not be fully integrated. Components are unreleased and may be fabricated and acquired through nonproduction techniques. These units are typically built by engineering and are not for sale to customers.

alpha build, software – A software build that contains prototypes or incomplete features in regards to the product specification. This type of software build is typically used by engineering to support hardware or electrical development during design phase or to prototype designs for review by the project team.

alpha design documentation – Detailed documents which are used to build or purchase components to construct the alpha prototype, including component specification sheets, assembly procedures, engineering drawings, and bills of materials.

alpha prototype assessment – A design review performed by the project team prior to purchase of components for the beta prototypes. The intent is to confirm a high confidence level in the integrity of the design and to establish back-up plans prior to making a significant investment in the purchase of beta prototype components. As a result of the assessment, action items are drafted and assigned to the appropriate team members and defects are corrected, as needed. If a change to the design is needed, it is reviewed and approved by the project manager, product manager, and project team members prior to its implementation.

beta and production unit forecast – The first year's forecast for all system requirements, including demonstration, customer units and all options.

beta build, hardware – Fully integrated, functioning system(s) with respect to the product specifications and preliminary manufacturing performance specifications. These units are composed of parts that are procured through standard production methods. These units should be built primarily by manufacturing, with minimal involvement of engineering. These should be built as a first test of manufacturing fixtures, documentation and process(es). It is usually acceptable to equip beta prototype units with alpha level software. Units are not for sale to customers unless refurbished to production level.

beta build, software – A versioned software release that contains one or more completed design specifications. The beta releases notes will indicate which of the items in the product specification are ready for verification. The software build must be designated as medium or higher quality if built by the automated build process. The software build must meet the quality requirements for internal testers in the test plan if it is not built by the automated build process. Beta software builds shall be labeled in the source code control system.

beta design documentation – The information from engineering that is required to be able to fully document (e.g., part drawings, preliminary assembly drawings, preliminary manufacturing details, bills of material, etc.) the beta system configuration that will be built into beta units.

beta manufacturing documentation and tooling – Hardware and software specifically designed to enable fabrication, simplify assembly, and expedite testing during production. This tooling can include molds, dies, jigs, assembly fixtures, material handling equipment, test macro software, and workflows.

beta manufacturing test plan – A document that describes the strategy for testing production units in the most cost-effective way to ensure that the device meets specifications. Includes plans for functional, and system testing operations and details requirements for special manufacturing tooling.

beta manufacturing test specifications – A detailed description of the tests with acceptance limits which determine if the performance characteristics of the Beta prototype are sufficient.

beta prototype assessment – A design review performed by the project team prior to purchase of components for the pilot build. The intent is to confirm a high confidence level in the integrity of the design and to establish back-up plans prior to making a significant investment in the purchase of pilot build components. As a result of the assessment, action items are drafted and assigned to the appropriate team members and defects are corrected, as needed. If a change to the design is needed, it is reviewed and approved by the project manager, product manager, and project team members prior to its implementation.

beta testing, hardware – Verification testing to confirm that the beta prototype hardware meets or exceeds the performance specifications, as established in the traceability matrix.

beta testing, software – Verification testing to confirm that the beta software meets or exceeds the software specifications.

business plan – A collection of plans that address a variety of business areas. The following plans are included in the business plan: marketing plan, financial plan, introduction plan, service plan, distribution plan, and product retirement plan. The business plan should describe any assumptions made about the product or market and assess the strategic, technical, support, financial, marketing, competitive and distribution risks. The plan should also note any potential patent infringement risks and possible technologies that could be patented. The business plan shall be reviewed and approved during the PMT Concept Phase to Design Phase approval process.

capital budget –Items needed to design or manufacture a product and their associated costs. These items have a value of at least $1,000 and an expected life of three years or longer. The project team should work with the CMSE to ensure that these budget items are included in the annual operations capital budget.

CCN – See **change control notice**.

change control notice – The process which Thermo Electron uses to control the release and change of product. It is governed by internal quality procedure.

CMSE – See **Customer and Manufacturing Support Engineering**.

concept model, drawings, etc. – A mockup depicting the general "look and feel" of the product. This can include concept sketches, physical models, and software models. The model indicates human factor concepts, design direction or innovation and mechanical constraints. Software models can use block diagrams, storyboards, and screens. The concept models shall be created with input from the customer, marketing, sales, engineering, CMSE, regulatory affairs, service, and project team. The project manager shall assign appropriate team members to evaluate and test the model(s).

concept phase – The third phase of the product development process during which the critical product, project and process elements of the project are defined. The key activities in the Concept Phase include minimizing risk in the Design Phase schedule and completing the traceability matrix. The traceability matrix details the product design specifications along with test plans. The Design Phase budget and the business plan are also important deliverables.

concept phase review – A documented, comprehensive examination of the project plan conducted by a cross functional team from engineering and CMSE. The review should ensure that the technical risks have been properly addressed. Possible results of the review are 1) a recommendation that the project is ready to proceed to the Design Phase from a technical point of view; 2) a list of outstanding issues to be addressed by the Project Team with an additional review of these issues to follow; or 3) a request for another review.

concept phase schedule – A detailed Concept Phase timeline that includes resource assignments, major and minor milestones, and interdependencies among related project tasks. Key items for the project team to consider are the resource and time impacts of the issues that are identified in the risk mitigation study and report, especially from technical and schedule risk perspectives. The project team should consider prototyping and/or testing the methods or designs in the Concept Phase that will need to be implemented in the Design Phase to achieve the product requirements.

configuration guide – A marketing document that establishes the various configurations of the unit that will be made available for sale to the customer. This document should include all appropriate options available with the product.

configuration guide, final proof – Final version of this document, used to sell the product. The document will include product number(s) and pricing information.

configuration guide, preliminary – First version of the document that establishes the various configurations of the product that will be made available for sale to the customer. Created in the Concept Phase., the document may include product numbers, but will not have pricing information.

critical supplier agreements – Agreements that are deemed necessary by the critical nature of the product supplied or position of the supplier. These agreements typically would include detail regarding performance objectives (cost, quality, delivery, continuous improvement, failure to perform), manufacturing rights, exit clauses, OEM agreements, and joint development agreements.

critical supplier risks – Identifies vendors of parts or processes to the product that are not easily substituted and potential vendor risks. The vendor may be unique or the capital expense and lead time in changing vendors may be prohibitive. Critical suppliers are typically determined during the Concept Phase by team members from engineering, manufacturing, purchasing, and materials quality.

Customer and Manufacturing Support Engineering (CMSE) – Group supporting products from inception to retirement, providing training and engineering support to internal and external customers. CMSE supports product design, development, and service with three focus areas:

> **Process CMSE** provides technical and process support to the personnel and systems in the various manufacturing work centers. Primarily focused on assembly and test procedures, processes, and equipment which are independent of specific end products.
>
> **Product CMSE** provides product or system level support to manufacturing personnel, field service personnel and the end user.
>
> **Project CMSE** provides project management to new product development. This group provides scheduling, manufacturing and service interaction, bill-of-material development, and vendor interface. This group ensures that regulatory requirements are met. During product development, this group will ensure that communications are open between the new product development team and all of manufacturing and customer support.

The efforts of all three areas are closely coordinated to ensure that all products are introduced and supported in a coherent manner.

design documentation –The physical output, or deliverable, of the design process that clearly specifies both the purchased components and the manufacture of the product. For each component, this will include a product master data sheet and either a specification sheet or a drawing. Design documentation for the manufacture of the product will include schematics, board layouts, source code, CAD assembly drawings, and manufacturing guidelines. The CAD assembly drawings created in the design process provide the conceptual basis for a structured bill of material and will be utilized as a starting point in creating the manufacturing assembly documentation. Manufacturing guidelines describe any specialized processes, procedures or steps required in the fabrication, assembly or testing of the product.

design documentation, complete –Design documentation for a purchased component will only be considered complete when the item has been successfully entered into the item master database. The project manager (or a designee) along with the CMSE team member will verify that the design documentation has been completed.

design history file (DHF) – A compilation of records that describes the design history of a finished product. The DHF covers the design activities used to develop the device, accessories, major components, labeling, packaging, and production process. Typical documents include: requirement documents, ROI, budget, resource allocation, meeting minutes, design review meeting minutes and dispositions, PDP checklist (signed and dated), source code, design documentation, test reports, user documentation, service documentation, quality audit results, lessons learned report, sketches, drawings, photos, engineering notebooks, component qualification information, verification protocols and data, prototype verification protocols and data, consultant information, traceability matrix, design output and validation documentation. It may include laboratory notebooks, memoranda and electronic mail correspondence. Items that are not signed or filled in by hand may be archived via computer optical media (e.g., CD-RW disks, etc.). Items must be easily retrievable, but are not required to be kept in one common place.

design input – The physical and performance requirements of a device that are used as a basis for the device design. This is also known as the product specification in the traceability matrix.

design output – Documented, reviewed and approved results of a design effort at each of the design phases and at the end of the total design effort. The total finished design output consists of the device, its packaging, labeling and the design history file.

design phase – The fourth phase of the product development process during which the project team defines, builds, debugs, verifies and validates the product in accordance with the product specification.

design phase review – A major design review of the beta prototype and/or pilot build test results and manufacturing process documentation to verify the design is ready to transfer to manufacturing. The purpose of the review is to ensure that the beta prototype has been properly verified against the product requirements and product specification and has been properly tested according to the project test plan. The result of the review will be either a recommendation that the project is ready to proceed to the Launch Phase from a technical point of view or a list of outstanding issues to be addressed by the project team with an additional review of these issues to follow.

design review – A documented comprehensive examination of a design to evaluate the adequacy of the design requirements to evaluate the capability of the design to meet these requirements and to identify problems. Major design reviews include members of the project team, engineering, CMSE, manufacturing, marketing and service. Minor design reviews include members of the project team.

design specification – Detailed description of how the project team will accomplish the product specification with an emphasis on the technical aspects. Each element of the design specification is traceable to one or more items in the traceability matrix.

design specification risk mitigation – All designs have inherent implementation risks. Risk mitigation outlines the known risks and indicates how they will be addressed during the Design Phase. The project manager and/or the project team shall review the product requirements to identify major risks in important functional areas including usability, reliability, serviceability, manufacturability, and regulatory approval.

DHF – See **design history file**.

discovery phase – The second phase of the project development process during which the potential of a new product idea is evaluated. The product manager is responsible for a majority of the deliverables during the discovery phase of a project. Required activities include a vision statement, preliminary ROI and PMT approval to Concept Phase. The product manager reviews required deliverables on the PDP checklist with the project manager and appropriate team members before entering into the Discovery Phase. The product manager, the project manager and the team determine which of the optional Discovery Phase activities shall be performed. The project manager reviews the marketing documents and compiles a Concept Phase schedule, budget and a list of requested resources. When the activities leading up to the Discovery Phase review are complete, the review is held. The marketing documents are reviewed and updated according to the review team decisions.

discovery phase review(s) – A marketing peer review of the Discovery Phase deliverables. This review examines the vision statement, market/competitive analysis, preliminary support plan, preliminary distribution plan, marketing product requirements, preliminary ROI and the preliminary marketing plan. The purpose of this meeting is to filter out projects that the marketing groups feel do not merit further work and to help refine the Discovery Phase deliverables.

distribution plan – A document that defines how the product will be distributed on a domestic and/or international basis, with specific consideration given to distribution channel design. The distribution plan is a subset of the business plan. Any distribution activities that are not currently employed should be described in this plan.

distribution training – The activities involved in properly training the sales staff and representatives on a worldwide basis. This training usually includes hands-on experience with the product as well as a detailed explanation of the specifications, applications and sales literature, and other collateral materials.

engineering prototype – Partially functioning system or set of subsystems with respect to the product specifications. This prototype may not be fully functioning with respect to the functional specifications, yet is used to test basic system or subsystem functionality. Components are designated NR (not released) and may be fabricated and acquired through nonproduction techniques.

extended team – All multifunctional resources who participate in the development of a new product and the introduction of that product into the marketplace. This might include members of engineering, manufacturing, marketing, service, training and sales.

failure analysis – Analysis performed on components, subassemblies, or systems to determine failure mode and frequency. Data from this type of analysis is used in determining mean time between failures and least replaceable units (LRUs).

introduction plan – A document that contains a well-defined strategy for internal/external product announcement and worldwide sales and marketing introduction. The preliminary introduction plan may include the following: product retirement plan (for existing product), plan for introduction to sales force, advertising plan, schedule for first orders and shipments, product literature requirements, plans for sales promotions and applications demonstrations, application notes, shows, technical papers, and presentations. The introduction plan is a subset of the business plan.

launch phase – The fifth phase the project development process during which the product is readied for full release to the marketplace, is introduced to the sales force, and offered for sale to the customer. The first customer shipment occurs during this phase, and the quality of the shipped product is monitored through product watch activities.

launch phase review – A formal review of the project deliverables, the quality audit responses and the Project Design History file.

least replaceable unit (LRU) – The smallest component or subassembly designed to be repaired or replaced in the field by the user or service personnel. User and service documentation provide information to support the product to this level. Typically, field repair to a lower level is not cost effective because of extended knowledge and/or special tools needed to perform the repair.

line management – Those individuals whose job description indicates responsibility for direct supervision of other employees.

LRU – See **least replaceable unit**.

manufacturing plan – The section of the business plan that identifies the methods used to manufacture of the product. The plan should identify new internal and external processes, capital fixturing and tooling, manufacturing risks, capacity limitations, training requirements, and beta and pilot run quantities. The manufacturing plan can include but is not limited to labor, space, new technologies, specialty tools, training, manufacturing details, system configuration, fixtures, production, final test and network issues.

manufacturing process documentation – Documents that describe how to manufacture and deliver the product as described in the design documentation.

manufacturing test plan – A document that describes the strategy for testing production units in the most cost-effective way to ensure that the device meets specifications. Includes plans for ATE, functional, and system testing operations and details requirements for special manufacturing tooling.

manufacturing test specifications – The manufacturing test specifications are the tests and acceptance criteria which determine if the performance characteristics of a manufactured product are sufficient to allow shipment.

manufacturing tooling – Hardware and software specifically designed to enable fabrication, simplify assembly, and expedite testing during production. This tooling can include molds, dies, jigs, assembly fixtures, material handling equipment, test macro software, and workflows.

market analysis – The market analysis compares and contrasts the proposed product with similar competitive products. This comparison often includes competitors' product literature and takes the form of feature, configuration, and pricing grids.

market research – Appropriate members of the team use various methods such as customer surveys, customer visits, and customer panels to develop a more fundamental understanding of the market needs.

marketing plan – A collection of analyses and plans including an introduction, product overview, vision statement, market analysis, strategic product profile, customer benefit analysis and competitive analysis. The marketing plan is a subset of the business plan.

marketing product requirements – A description of the characteristics and intended use for the product, written as more of a qualitative document than a quantitative document. For example, the term “must be portable” is appropriate for a marketing requirements document because it raises questions about size, weight, resistance to shock and vibration that will then be quantitatively described in measurable terms in the product specification. The marketing product requirements document is the first of the requirements documents created during a project. This is an uncontrolled document.

owner – Person responsible for seeing that a task is completed.

patent submittals – In the course of the design phase, valuable patent positions may be identified in the product design. The project manager should work with the technology development group to determine if there are potentially patentable items in the design.

PDP – See **product development process**.

PDP checklist – A product development document used to identify the project deliverables for each project phase. The checklist identifies the deliverable, owner, reference form number (if applicable), completion date, signature and comments. When the deliverables acceptance criteria are satisfied, the owner may sign and date the checklist. The project manager and the team shall review the PDP checklist. It is up to the team to determine the appropriate deliverables for the project, in addition to those required. All phase activities will be designated as Yes, No or TBD (to be determined), as required by task. The project manger or designee shall document, sign and date all changes to the requirements section of the PDP checklist. At the end of the project, all TBDs should be changed to either a Yes or a No.

PDP quality audit – The quality audit is a review process that occurs when a product is ready for first customer shipment. The quality audit attempts to review aspects of a product as they would be observed by a customer. Typically, a mock order for the product is placed and delivered to an internal location. A service engineer installs the product, and the audit team reviews the quality of the product, packaging, completeness, and operation. The output document indicate s observed quality issues that the project team must address. Noncompliance issues from the quality audit will have to be resolved before the first shipment to a customer.

pilot build, hardware – The initial production units used to confirm the entire manufacturing process. The pilot run units are composed of parts that are under manufacturing revision control, fabricated by production vendors, purchased through standard channels, assembled by production technicians using manufacturing tooling, and tested to the manufacturing test specifications by production test technicians.

pilot build, software – The media produced to confirm the entire software manufacturing process. The media are composed of parts that are under manufacturing revision control, fabricated by production vendors, purchased through standard channels, and assembled by production technicians using manufacturing tooling and equipment.

PMT – See **portfolio management team**.

PMT project approval – A meeting between the PMT and the project and product managers who completed the approval documents. The Portfolio Management Team (PMT) consists of a group of senior managers who approve and prioritize the development projects that are currently active. This approval deliverable is required on all projects. The PMT may approve the project into the Discovery Phase , request further pre-approval work, or reject the project.

portfolio management team (PMT) – The highest-ranking management team responsible for managing the product portfolio matrix and pipeline. Typically, a PMT review is required at each phase of every project before proceeding to the next phase.

portfolio matrix – A product development tool that shows the priority, resource leveling, and timeline by phase for approved projects.

product development process (PDP) – The process that Thermo Electron's Madison, Wisconsin site uses to develop new or improved products. The PDP is a documented design control process to determine user requirements and regulatory standards, develop specifications, labels, packaging, manufacturing process specifications, and manufacturing facilities, select and evaluate components and suppliers, and verify and validate the final design. The PDP has five phases which include: Project Approval, Discovery, Concept, Design, and Launch. There are two phases that occur after the product has moved on from the Launch Phase. These are: Sustaining Phase and Retirement Phase. These activities are not governed by the PDP process, but are listed for reference purposes.

product literature – Electronic, printed and website tools to assist ongoing marketing and sales efforts for the product. Product literature can include product brochures, application notes, marketing performance specifications, performance evaluations, configuration and pricing information, competitive analyses, and sales training aids.

product manager – Team member responsible for the business aspects of the product during development. The product manager establishes the vision statement and initial product specification, product validation requirements, and product configurations. The product manager and the project manager work together in all phases of the project to ensure that the project's objectives are met.

product release CCN – The action by which parts become released. Prior to this point the part numbers are tagged in the item master database as PNR (meaning Part Not Released) or NR (meaning Not Released). Parts are released by the CMSE Product team member

product requirements – The physical and performance requirements of a device that are used as a basis and input for the product specification, a key part of the traceability matrix. Requirements may come from all functional areas of the company including marketing, regulatory, documentation, labeling, shipping, service, hardware, software, firmware, maintenance, warranty and manufacturing. Design input includes determining customer needs, expectations and requirements, plus determining regulatory, standards and other appropriate requirements.

product retirement plan, preliminary – A document that addresses the eventual retirement of a released product. Retirement generally progresses through three phases of product support: full, partial, and no support. When a product is retired, all continuing engineering and service support are suspended. The plan also indicates when the customers will be notified that the product will no longer be serviced. The product retirement plan is a subset of the business plan.

product specification – The product specification is contained in the traceability matrix. It is a complete description of the product to be developed. Each item in the product specification shall be assigned an identifying number and maintained in the traceability matrix. Each item in the specification shall be traced to a design specification, a test plan item, acceptance criteria, and documented test results. The product specification consists of functional specifications, performance specifications, regulatory approval needs, technical writing requirements, warranty and installation requirements, targeted cost of goods, labeling, manufacturing, installation, maintenance, service, desired release date, and any other special requirements. The product specification shall be reviewed and revised to remove any incomplete, ambiguous or conflicting requirements. The product specification shall be documented and shall be reviewed and approved by designated team members. The approval, including the date and signature of the individuals approving the specification, shall be documented.

product standards compliance – A determination that the mechanical operation, electrical functioning, electromagnetic compatibility and labeling of a given product meets minimum mandatory or voluntary requirements. Product standards compliance is based on actual tests or inspections of a product according to documented test protocols having pass/fail criteria. An applicable product standard may include requirements for radiation emission (electromagnetic, X-ray, laser, ultrasound, etc.), electromagnetic immunity, static protection, flame retardant capacity, tip-over susceptibility, warning label content, etc., and may come from standards organizations such as ANSI, UL, IEC, FDA, or CSA, from trade organizations or industry practices; or from customer expectations and internal design criteria.

product status disclosure for showing, demonstration – Before showing or demonstrating an alpha or beta version of a product to potential customers or sales staff, this document should be generated and approved. The intended use of the document is to establish a full understanding between the project team, the product manager (and marketing group, if required) about what is to be shown to the sales force or the public. This document spells out what product features are missing, what features are not fully debugged, and what is not functional on the product being displayed. It also specifically lists any cosmetic anomalies, special installation, operation, handling and/or presentation instructions, and what will be tested on the product prior to shipment and by whom. This document will refer to a specific number of showings or demonstrations.

product watch – A process managed by the technical support group monitoring the introduction of a new product in the market place. Product watch ensures that a new product is meeting product specifications and expectations for reliability, usability, and performance. Product watch starts with the first customer shipment.

product watch report – A summary of the status of the product at the end of the Launch Phase. The product watch report outlines any outstanding quality issues reported from Manufacturing and from field service, and how they are being addressed. The product watch report is reviewed at the Launch Phase review prior to the PMT Launch Phase to Sustaining Phase approval.

production units – A product manufactured under manufacturing revision control using standard manufacturing procedures. These units consistently meet manufacturing performance specifications and are sold to customers.

project approval phase – The first phase of the product development process during which an idea for a new project is formulated, discussed, documented and approved to enter the Discovery Phase. These activities are directed by the product manager. An initial project manager is assigned to work with the marketing staff member to develop the estimated ROI for the project.

project budget – The compilation of expenses that will provide the project with a successful outcome. This includes such things as labor costs, professional services, engineering prototyping expenses, beta unit costs, travel, capital expenses.

project file – A collection of documents which verify that the deliverables required by the Product Development Process (PDP) were completed. The following documents must be filed in the project file: project phase authorization forms and the required attachments, PDP checklist, product specifications, quality issues records, business plan elements, project plan elements, product watch reports, quality issues records, meeting minutes, design review minutes and review approvals. Additional documents may be kept in the project file for historical purposes.

project manager – The project team member responsible for the technical aspects of the product and project administration details during the entire product development effort.

project plan – A collection of documents that details how the project is to be organized and operated to facilitate the design. The project plan includes, but is not limited to, the project budget, capital budget, technical writing plan, translation plan (this may be part of the technical writing plan), technology introduction plan, project schedule and traceability matrix. The project plan is reviewed and approved during the Concept Phase Review.

project retrospective assessment – A project development activity directed by an assigned facilitator to review, discuss and document positive and negative project activities. This is not meant as a fault-finding exercise but rather as an analysis for future improvements. The facilitator will identify applicable lessons learned, and these items will be discussed, documented, and tracked. If necessary, a mitigation plan may be established. Project retrospective will most likely affect project scope, budget, time and performance.

project schedule – A detailed project timeline that includes resource assignments, major and minor milestones, and interdependencies among related project tasks.

project team – A cross-functional team from ns critical functional areas involved in the development project. The project team is formed at the beginning of the Concept Phase and generally remains intact through the Launch Phase. Included on the team are the product manager, the project manager, and appropriate representatives from engineering, CMSE, applications, and document development, as established by the project manager. Larger projects may also include a lead software engineer, a lead hardware engineer, a lead firmware engineer and a representative from the purchasing group. The project manager selects the project team, and the engineering group and each of the supervisors of the members of the team must approve the selections.

quality – The totality of features and characteristics that impact the ability of a device to satisfy fitness-for-use, including safety and performance.

quality audit lead – A person who leads the quality audit team and ensures that all quality audit noncompliance issues have been documented prior to approving the quality audit report.

quality issues record –A document that records quality-related project issues which need to be communicated to team members to ensure that they are addressed. The resolution of each recorded issue must be documented in a subsequent quality issues record. A quality issues record can take the form of meeting minutes or a log of issues, and should be updated on a regular basis. The quality issues records for each project can be found in the project file in either paper or electronic form.

quality system – The organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

regulatory approval submissions – A determination that a product may be legally marketed in a given territory. This may involve statutory requirements of a particular territory as well as regulatory requirements. This activity may involve sending the product to an outside facility for testing, brining in a consultant for an audit, or self-certifying the system. The project manager works with the regulatory manufacturing engineer to establish a strategy for attaining regulatory approvals and scheduling the testing.

regulatory approvals – Once the product has been successfully tested against all applicable regulatory and statutory requirements and granted the appropriate approvals in specific markets, it can be legally marketed and distributed to those markets.

released – The formal transfer of documentation to manufacturing revision control. This may include documents describing components, subassemblies, assemblies, software, and manuals.

resource – Labor and equipment required to perform a given task.

return on investment (ROI) – A calculation of the percent return the potential product will bring. The calculated value is a percentage that indicates the profitability of the product over 4-5 years versus the costs of goods, development costs and other expenses. This deliverable is required on all projects. The master spreadsheet used for this calculation is maintained by accounting staff who are available to help the project and product managers complete the spreadsheet properly.

risk – A condition that could jeopardize the future viability of the project or product. Areas that may involve risk are: technical (hardware, software, mechanical, regulatory approval), financial, marketing, distribution, competition (internal and external), service, manufacturing, purchasing and legal (patent, copyright infringements, insurability). Impact of risks should be designated significant, moderate, minimal or none. Probability of the risk occurring should be designated highly likely, possible or highly unlikely.

risk mitigation study and report – A document that identifies risks associated with new technologies and suppliers if included in a new product design. Provides alternatives if the new technology is unsuccessful. This report may summarize the findings and results of the risk mitigation study, qualify the levels of risk, and establish the probability of occurrence. New technologies are those that are known but outside current technology strategies, unknown or not fully developed to date. This report should also include schedule risks. This is a precursor to the generation of the Traceability Matrix.

ROI – See **return on investment**.

service diagnostics – Procedures and any necessary hardware and/or software required to accurately diagnose instrument problems in the field. They may be intended for use by customers or trained service engineers. Beta versions are tested against the product specifications outlined in the traceability matrix.

service documentation – Collection of documents required to install and support the product. This includes the service manual, LRU list, price list, contract information, installation procedure, preventive maintenance checklist, upgrade procedures, and technical bulletins.

service plan – A document describing the strategy for installing and supporting the product. This document usually includes the service philosophy, warranty information, spares policy (LRUs), service training requirements, service contract information, installation requirements and upgrade paths.

service training – The activities involved in training the worldwide service group to properly install, service and maintain the product.

software release candidate – Before showing or demonstrating an alpha or beta version of a product to sales staff or potential customers, this document should be generated and approved. This is intended to establish a full understanding between the project team and the product manager (and the marketing group, as required) about what is to be shown to the sales force or the public. This document spells out what product features are missing, what features are not fully debugged, and what is not functional on the product being displayed. It also specifically lists any cosmetic anomalies, special installation, operation, handling and/or presentation instructions, and what will be tested on the product prior to shipment and by whom.

specification – Any requirement with which a product, process, service or other activity must conform.

statutory requirements – Product requirements related to the legal constraints of marketing the product in a specific territory or country.

supplier research – Determining which vendors can address the various key aspects of the project. This activity may entail using existing vendors or locating new vendors. The goal is to establish a working relationship with the vendors as early as possible, to facilitate working towards concurrent development activities.

support plan – The section of the business plan that identifies the methods for supporting the product. The plan should identify new internal and external processes, capital tooling, service risks, capacity limitations, training requirements, fixturing requirements, and technical support issues.

system integration – The process of combining hardware, electronics and software to produce a working prototype with respect to the functional specifications. This process is usually performed on an engineering prototype, transforming it into an alpha prototype.

technical writing plan – This plan should identify the documents required (for example, user manual, safety manual, pre-installation manual, on-line users manual), provide estimated page count and manual type (for example, spiral bound, on-line), and determine whether illustrations are required. The plan should state the intended audience, media type, and style for each technical writing requirement and include a resource estimate for each requirement, listing page counts and the amount of time required from technical writers and illustrators.

test protocol – A test protocol that is used by software to ensure compliance of a given software feature to the software specification.

traceability matrix – A documented trail, typically in a spreadsheet, that shows the link from a product specification to a design specification item or items, to a test plan, to the test results and acceptance criteria. In its most common form, the product requirements are enumerated (tagged) in a table (spreadsheet), and references are provided to each section in the design specification which addresses or satisfies the requirement. Each item in the matrix shall be given a unique number. The matrix includes a section documenting verification activities assigned to individuals and allowing for signing those completed. Separate sections document validation and introduction activities.

translation plan – A document that details how product documentation, software text, labels, etc. will be translated to other languages. Translation requirements are defined in the project plan and associated design considerations are covered in the design specification. The translation plan should include the priority and languages for each document, software package and label set. The plan should indicate an estimated preliminary cost for each translated document and label set. This plan may be part of the technical writing plan.

usability – A product is usable when it provides the functionality that the intended users need, is designed from the users' perspective, is reliable, easy to learn and use, and protects users and data.

user documentation – Any document (printed or on-screen) intended to be used by the customer. The product user documentation consists of a set of documents that describe the site requirements, safety implications and operation of the product. User documentation goes through several review cycles. Reviewers should generally include the engineering, applications, marketing and the CSME team members.

validation – Confirmation by examination and objective evidence that the product specifications for specific intended end use can be consistently fulfilled. The purpose of this is to show that the product specifications fulfill the user's needs for its specific intended end use.

validation specification – A listing of intended uses and expectations of a product that needs to be tested to ensure that the product meets customer requirements.

validation test plan – Confirmation by examination and objective evidence that the product specifications for specific intended end use can be consistently fulfilled. This shall include software validation, where appropriate. The results of the design validation, including identification of the design, method, date, individuals performing the evaluation shall be documented in the design history file.

validation test plan review – A meeting to review the plan for the product validation tests.

validation test results review – A review of the design output and final device to verify the design output meets the requirements of the design input and validates the final product meets the marketing product requirements and user needs.

verification – Confirmation by examination of objective evidence that product specifications in the traceability matrix have been fulfilled.

verification test plan – A plan for confirmation by examination of objective evidence that product specifications have been fulfilled. This shall confirm that the design output meets the product specification.

verification test plan review – A review of the verification test plan to assure that the plan is complete and comprehensive.

verification test results review – A review of the verification test results to ensure the results conform with the performance specification. The results of the design verification, including identification of the design, method(s), the date and the individual performing the verification shall be documented using a traceability matrix in the design history file. Objective evidence refers to the results gathered for the acceptance criteria. If required (see PDP checklist), the project manager or designee will prepare the verification test results for review.

vision statement – This statement will describe the scope of the new product at the time of authoring the document including how the new product will fit in with the rest of the product line. This document is generated by marketing in the Discovery Phase. This broad description leads into the more specific marketing product requirements and then into the product specification columns in the traceability matrix.

Chapter 10 Certificates

This chapter contains samples of certificates and declarations of quality and qualification:

- Thermo Electron Corporation's Madison Wisconsin site ISO 9001:2000 certificate states that the site (also known as Thermo Electron Scientific Instruments Corporation) has been certified by KEMA – Registered Quality, Inc., an outside accrediting agency, to meet the ISO 9001 requirements.

- The Declaration of System Qualification certifies that software and hardware products developed by Thermo Electron Corporation's Madison, Wisconsin site have been designed, tested, and manufactured in accordance with our ISO 9001 Product Development Procedures.

ISO 9001 Certificate, Thermo Electron's Madison, WI site

KEMA

Affiliate with the N. V. KEMA in the Netherlands
A member of the International Network for Quality System Assessment and Certification "IQNet"

CERTIFICATE

Number: 10018.05

The Quality System of:

Thermo Electron Scientific Instruments Corporation
5225 Verona Road
Madison, WI 53711

Including its implementation, meets the requirements of the standard:

ISO 9001:2000

Scope:
The design, manufacture and service of spectroscopy instrumentation and accessories used in chemical research, quality assurance and process control of materials.

This Certificate is valid until:	December 3, 2004
Renewal Date:	December 3, 2001
Revision Date:	April 21, 2003
Issued for the first time:	March 8, 1995

H. Pierre Sallé
President
KEMA-Registered Quality, Inc.

The method of operation for quality certification is defined in the KRQ General Terms and Conditions for Quality Certification. Integral publication of this certificate and adjoining reports is allowed.

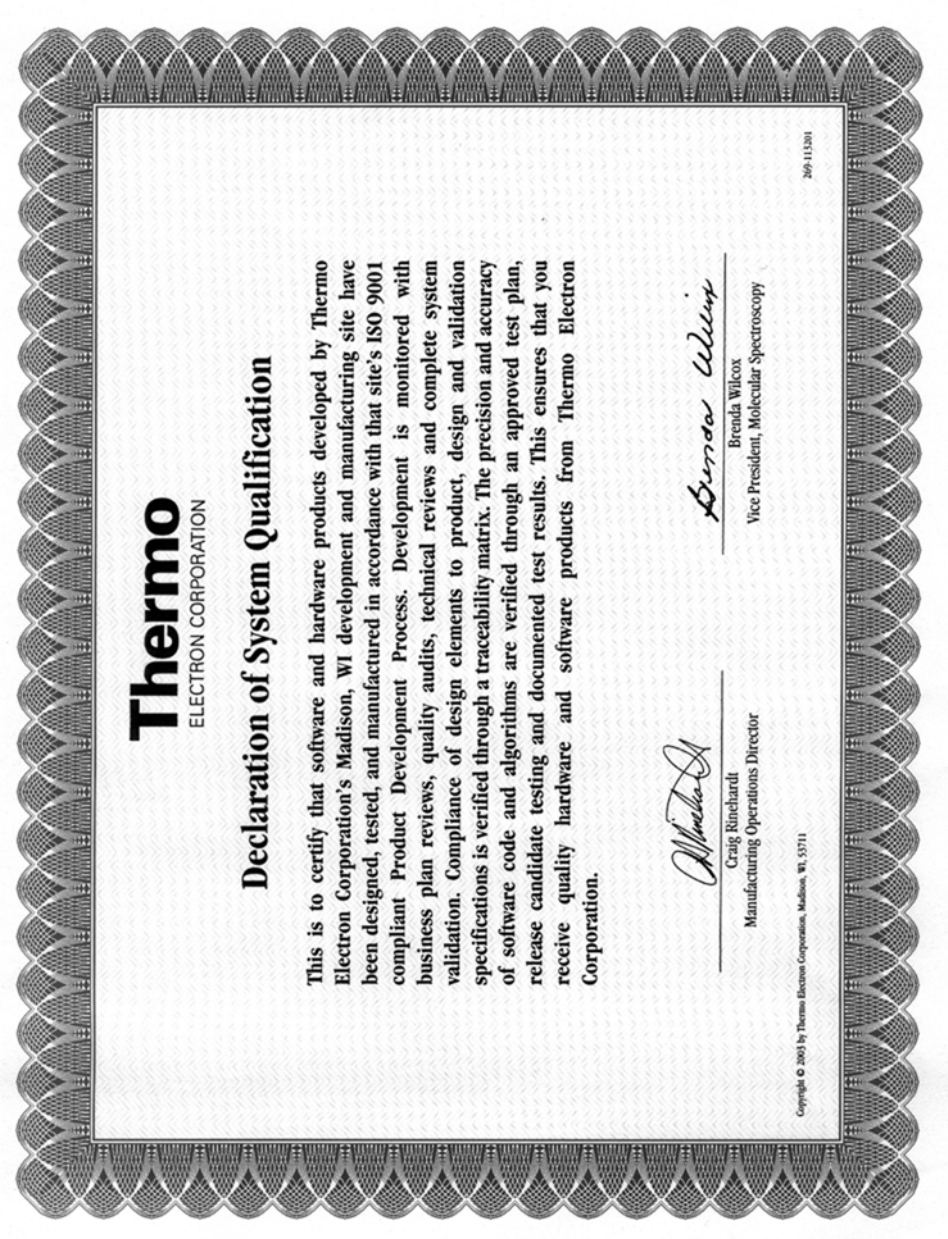
KEMA-Registered Quality
4377 County Line Road
Suite 202
Chalfont, PA 18914
Ph: (215) 997-4519
Fax (215) 997-3809

Accredited By:
ANSI-RAB NAP
The Dutch Council for Accreditation (RvA)

ANSI-RAB QMS ACCREDITED

MGMT. SYS.
RvA C 099

Certificate of System Qualification – Sample



Thermo
ELECTRON CORPORATION

Declaration of System Qualification

This is to certify that software and hardware products developed by Thermo Electron Corporation's Madison, WI development and manufacturing site have been designed, tested, and manufactured in accordance with that site's ISO 9001 compliant Product Development Process. Development is monitored with business plan reviews, quality audits, technical reviews and complete system validation. Compliance of design elements to product, design and validation specifications is verified through a traceability matrix. The precision and accuracy of software code and algorithms are verified through an approved test plan, release candidate testing and documented test results. This ensures that you receive quality hardware and software products from Thermo Electron Corporation.

Craig Rinehardt
Manufacturing Operations Director

Brenda Wilcox
Vice President, Molecular Spectroscopy

269-113201

269-111501

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