

Unit 5: Quality Management Systems

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5.1 The concept of quality

Every practice in this subject is a servant of one idea, and Unit 5 finally names it. **Quality** in the pharmaceutical sense is not luxury or excellence in the abstract; it is the **fitness of a product for its intended use**, expressed by the standard definition used across the ISO family: the degree to which a set of inherent characteristics fulfils requirements. For a medicine, the requirements are unforgiving and mostly invisible to the user: correct identity, strength, purity, and performance in the patient, batch after batch, for the whole shelf life, for every patient, most of whom will never know a batch number. Because the patient cannot test the tablet, quality cannot be inspected into the product at the end (a tested sample proves something about the sample and, statistically, the batch; it cannot repair the batch), and so the discipline's founding maxim follows: **quality should be built into the product, and testing alone is not enough**. That sentence, which appears in substance in ICH Q10, is the intellectual charter of this entire subject: GMP builds quality into manufacture, GLP into studies, GDP into distribution, and the quality management system is the organisation wide machinery for building rather than hoping.

5.2 Total Quality Management

Total Quality Management (TQM) is the management philosophy from which the modern pharmaceutical quality system descends. Its teachers (Deming, Juran, Crosby) gave it durable elements: **customer focus**, where the customer of each process step includes the next step and ultimately the patient; **total involvement**, quality as everyone's job rather than a department's; **process thinking**, managing the process that makes results rather than exhorting the people who inherit it; **continual improvement** in small verified cycles (the plan, do, check, act cycle); and **management by fact**, decisions from measured data rather than opinion. Deming's fourteen points and Juran's trilogy (quality planning, quality control, quality improvement) are the classic examination furniture. TQM's pharmaceutical descendant replaced its voluntary language with regulatory obligation: where TQM urges, ICH Q10 requires, but the genealogy is direct, and a student who presents Q10 as applied TQM under GMP law has understood both.

5.3 Quality by Design

Quality by Design (QbD) is TQM's process thinking made pharmaceutical and mathematical, defined in **ICH Q8** as a systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management. Its working elements form a chain every student should be able to walk: the **quality target product profile (QTPP)** states what the product must be; **critical quality attributes (CQAs)** name the measurable properties that must be controlled for the patient; risk assessment links material attributes and process parameters to those attributes and identifies the **critical process parameters (CPPs)**; designed experiments explore how parameters interact and establish a **design space**, the multidimensional region within which operation is assured to give quality (movement within an approved design space is not a change; movement out of it is); and a **control strategy** carries the knowledge into routine manufacture, with a life cycle of continual improvement under ICH Q10. QbD matters to a regulatory affairs student commercially as much as scientifically: a dossier written in QbD language, with design space and control strategy, is the modern form of the applications MRA102T and MRA201T handle, and regulators reward the

understanding it demonstrates with flexibility an old style dossier cannot claim.

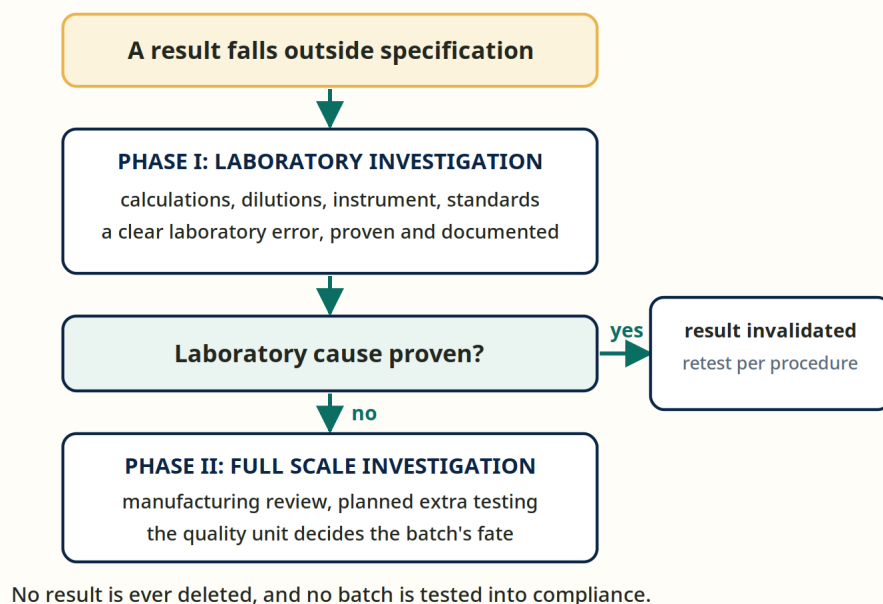
5.4 The Six Sigma concept

Six Sigma is quality management expressed as statistics. A process is described by its variation, measured in standard deviations (sigma) between its mean and its specification limits; the higher the sigma level, the rarer the defect, with the six sigma standard corresponding to about **3.4 defects per million opportunities** under the method's conventional allowance for long term process drift. The improvement engine is **DMAIC**: **Define** the problem and its critical to quality measures; **Measure** the current performance honestly; **Analyze** the data for root causes; **Improve** the process and verify the gain; **Control** the improved process so the gain is kept. (For designing new processes, the companion is DMADV.) In pharmaceutical quality work Six Sigma supplies the mathematics behind deviation reduction, yield improvement and complaint reduction programmes, and its belt system (yellow, green, black, master black) supplies the trained people. Its honest limitation belongs in an examination answer too: a sigma level is a statement about a defined process and measured data, and the method degenerates into ceremony where the measurement system itself is weak, which is why this subject teaches method validation (section 5.8) in the same unit.

5.5 Out of Specifications: handling the result that fails

An **Out of Specification (OOS)** result is a laboratory result that falls outside the established specification for its material or product. The handling of OOS results is where quality systems are most severely tested, because the temptation to test a failing batch into compliance is the exact sin GLP and GMP were written against, and regulators have the case law to prove it (the United States court judgment in the Barr Laboratories case of 1993 shaped the modern rules, and the FDA's guidance on investigating OOS results, issued in 2006 and revised since, is the working text). The disciplined sequence: **Phase I, the laboratory investigation**: the analyst and supervisor examine the obvious causes within the laboratory (calculation, dilution, instrument, standard, sample preparation), under pre written rules; if a clear laboratory error is proven and documented, the result is invalidated and a retest follows the procedure; averaging away, or quietly retesting until a pass appears, is prohibited. **Phase II, the full scale investigation**: if no laboratory cause is found, the investigation widens to manufacturing, with additional testing of retained samples under an approved plan, and the batch's disposition decided on the totality of evidence by the quality unit. Two neighbours must be kept distinct: an **out of trend (OOT)** result is within specification but against the expected pattern, a warning handled by trend review rather than the OOS procedure; and an atypical result in stability or in process data has its own handling. The principles that survive every version: no result is discarded without documented scientific cause, the original result is never deleted, and the quality unit, not the laboratory or production, owns the conclusion.

Handling an Out of Specification Result



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Figure: An out of specification result moves through a Phase I laboratory investigation and, if unexplained, a Phase II full scale investigation, with the quality unit deciding disposition.

Change control, step by step

Change proposed and described, with reason

- > Impact assessed: quality, safety, efficacy, validation, regulatory filing
- > Approvals taken, including regulatory approval where the filing requires it
- > Change implemented under plan, with training and document updates
- > Effectiveness checked after implementation, and the change closed

5.6 Change control

Nothing in a validated, registered process may simply be altered: the product the regulator approved is the product of a described process, and an uncontrolled change silently makes a different product. **Change control** is the formal system that governs alteration: a documented proposal describing the change and its justification; an **impact assessment** across quality, safety, efficacy, validation status, documentation and regulatory commitments (the same change can be trivial in the plant and major in the dossier, requiring prior approval from one authority, notification to another, and only internal approval for a third, the classification logic MRA102T meets as PAS, SUPAC and CBE categories); approval by the quality unit and affected functions before implementation; implementation under a plan with updated SOPs, specifications and training; and a post implementation review confirming the change did what it promised and nothing it should not. Temporary changes are controlled with expiry dates, emergency changes with retrospective documentation under strict limits. Change control is the connective tissue of this whole subject: it is how GMP absorbs improvement without losing registration, how validated computer systems evolve under GALP, and how the Validation Master Plan of the next section stays true.

5.7 Validation and qualification: types, and the Validation Master Plan

Validation is documented evidence that a process, procedure or method, when operated within established parameters, will consistently produce a product or result meeting its predetermined specifications; **qualification** is the same idea applied to premises, equipment and utilities (proving the instrument is fit), and validation is built on qualification. The **types of validation** by timing are the classic trio: **prospective**

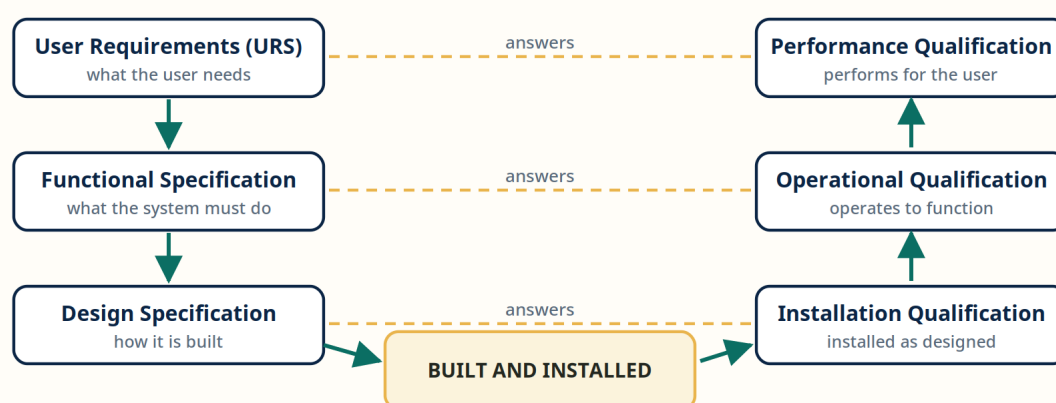
validation, completed before routine production on the basis of protocol driven studies (the modern default); **concurrent validation**, performed during routine production in exceptional, justified circumstances; and **retrospective validation**, based on accumulated historical data for old stable processes, now little accepted for new claims. By object, the family includes process validation (in its modern life cycle form: process design, process qualification, continued process verification, per the FDA's 2011 process validation guidance), cleaning validation (section 5.8), analytical method validation (section 5.8), and computer system validation (Unit 3). All of it is planned in one document: the **Validation Master Plan (VMP)**, the site's validation constitution, which lists what will be validated and qualified, the approach and acceptance criteria philosophy, responsibilities, documentation and scheduling, and the revalidation policy. An inspector who asks for the VMP is asking whether validation at this site is a system or a scrapbook.

5.8 Analytical method validation, utility validation and cleaning validation

Analytical method validation, governed by **ICH Q2**, proves a test method is fit for its purpose by measuring its performance characteristics: **accuracy** (closeness to the true value), **precision** (repeatability, intermediate precision and, where needed, reproducibility), **specificity** (the ability to measure the analyte undisturbed by everything else present), **linearity** and **range** (proportional response across the working interval), **detection limit** and **quantitation limit** (for impurity methods), and **robustness** (survival of small deliberate variations). Which characteristics are required depends on the method's job (identification, assay, impurity limit test, impurity quantitation), a matrix worth reproducing in an examination from Q2 itself.

The **validation of utilities** applies qualification to the invisible services: **water systems** (purified water and water for injection, qualified through design, commissioning and a phased sampling regime that proves chemical and microbiological control, then held under continuous monitoring, because water is the largest ingredient of most processes); **steam** (quality and dryness for sterilisation duty); **compressed air** (oil, water, particles and microbial quality at points of use); and **HVAC** (the heating, ventilation and air conditioning that delivers cleanroom air changes, pressure cascades, temperature and humidity, and is qualified with particle counts and recovery studies). **Cleaning validation** proves that cleaning procedures remove residues of the previous product, cleaning agents and microbial load to predetermined safe limits, classically derived from dose based criteria (a fraction, conventionally one thousandth, of the minimum therapeutic dose carried into the maximum daily dose of the next product) and the traditional 10 ppm and visually clean criteria, established on worst case products and hard to clean locations, with swab and rinse sampling. Together these three validation territories answer the inspector's deepest question: not whether today's batch passed, but whether the system can be trusted on the day nobody is watching.

The Validation V Model



Qualification proves each specification was met: IQ against design, OQ against function, PQ against the user's need in real use.

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Figure: The V model of qualification: each specification level on the left is answered by a qualification level on the right, from user requirements down to design and back up.

5.9 The ICH process and the ICH guideline families

The **International Council for Harmonisation (ICH)**, met in Unit 1's European and American frames and in MRA subjects throughout this branch, deserves its own section because Unit 5 names **the ICH process** itself. ICH was founded in 1990 (as the International Conference on Harmonisation, renamed when it became a legal association in 2015) by the regulators and industry associations of Europe, the United States and Japan, and has since widened to further regulators, including India's CDSCO as a member. Its method is deliberate: topics are chosen, an expert working group drafts a guideline through the **five steps** (consensus building, confirmation and adoption by the Assembly, regulatory consultation in each region, adoption of the harmonised guideline, and implementation in each region's law and guidance), and the result is one technical text that all member regulators accept. The guidelines are filed in **four families**: **Q, quality** (Q1 stability, Q2 analytical validation, Q3 impurities, Q6 specifications, Q7 GMP for active pharmaceutical ingredients, Q8 pharmaceutical development, Q9 quality risk management, Q10 pharmaceutical quality system, and their successors); **S, safety** (the nonclinical family, from carcinogenicity to genotoxicity); **E, efficacy** (the clinical family, including E6 good clinical practice); and **M, multidisciplinary** (M4, the Common Technical Document that MRA102T teaches, MedDRA, and electronic standards). The sentence that closes an examination answer on ICH: it establishes, in the syllabus's own words, the quality, safety and efficacy requirements of drug substances and products, so that a study, a validation or a dossier done once, to the harmonised text, can be read everywhere, which is the entire economic and ethical point of harmonisation: less duplication, faster access, no lower standard.

5.10 ISO 13485, Schedule M and CDSCO guidance: the closing frame

The unit closes where the subject began, with the device world and the home regulator. **ISO 13485** is the international quality management system standard for **medical devices**: a QMS built on ISO 9001's skeleton, specialised for devices with requirements for design control, sterile manufacture, risk management linkage to ISO 14971, and regulatory reporting; certification to ISO 13485 is the normal evidence of a device maker's quality system worldwide and the descendant of the GHTF SG3 work of Unit 1. Beside it the syllabus places **Schedule M** of India's Drugs and Cosmetics Rules (printed in the syllabus in the compressed form "Sch M III"), the Indian GMP code: Schedule M states the good manufacturing

practices for premises, plant and equipment for pharmaceutical products, and its recent revision aligns it more closely with WHO GMP; CDSCO administers it through the central and state inspectorates and publishes the guidance documents through which Indian manufacturers are judged, alongside the Medical Devices Rules 2017, which brought devices under a risk based Indian framework of their own. The regulatory affairs professional this subject is training will live between these frames for a career: international harmonised texts above, the Indian statute and CDSCO guidance at home, and ISO standards as the common technical language between them. Good Regulatory Practices is the foundation subject of the branch precisely because every later subject, documentation, clinical research regulations, Indian legislation, and the country by country regulatory aspects of Semester 2, is written in the vocabulary these five units have built.

Frequently Asked Questions

Q: What are the good regulatory practices, and which ones does MRA101T cover? They are the codified ways of working, the GxP family, that make pharmaceutical work acceptable to regulators: GMP for manufacturing, GLP for nonclinical laboratory studies, GCP for clinical trials, GALP for automated laboratory systems, GDP for distribution, and others such as GVP for pharmacovigilance. MRA101T teaches cGMP, GLP, GALP and GDP in depth, one unit each, and binds them together in Unit 5 with quality management systems, validation and the ICH process. GCP appears at the edges, since it belongs mainly to this branch's clinical research subjects.

Q: Why is the word "current" used in cGMP? To make the standard move with technology. When the United States revised its GMP regulations in 1978 it added "current" so that companies must use up to date technology and systems, not merely the practices that were acceptable when the text was written. A method that was good practice a generation ago, such as uncontrolled handwritten records where validated electronic systems now exist, can become a deficiency today without the regulation changing a word.

Q: What is the difference between 21 CFR Part 210 and Part 211? Part 210 states drug cGMP in general: the status and applicability of the regulations and the definitions, including the rule that a drug made outside cGMP is adulterated. Part 211 states the cGMP for finished pharmaceuticals in operational detail, in subparts covering organisation and personnel, buildings and facilities, equipment, control of components, production and process controls, packaging and labelling, holding and distribution, laboratory controls, records and reports, and returned and salvaged products. In short: 210 frames the law, 211 runs the factory.

Q: What do Articles 6 to 14 of Directive 91/356/EEC contain? They are the operative articles in which the European Commission's 1991 directive states the principles of GMP for human medicines: quality management, personnel, premises and equipment, documentation, production, quality control, contract manufacture and analysis, complaints and product recall, and self inspection. The directive has been recast since, and the principles are used today through EudraLex Volume 4, the EU GMP Guide, but the syllabus names the 1991 text because it states the principles in their cleanest short form.

Q: What is the role of the study director and the quality assurance unit in GLP? The study director is the single named individual responsible for the conduct of one nonclinical study and for its final report: approving the protocol, ensuring procedures are followed, judging deviations and signing the report as a true account. The quality assurance unit is independent of study conduct: it inspects studies at critical phases, audits the final report against the raw data, and places a signed QA statement in the report. The separation is the point: one person answers for doing the study, another for checking that it was done as reported.

Q: What is 21 CFR Part 11, and how does it relate to GALP? Part 11 is the FDA regulation of 1997 that accepts electronic records and electronic signatures in place of the paper records and handwritten signatures required by the predicate rules, when systems meet its controls: validation, audit trails, authority checks, record protection and signature controls. GALP is the broader good practice framework for automated laboratories, covering system documentation, security, training, change control and archiving. Part 11 gives GALP's principles legal force for FDA regulated records; GALP gives Part 11 its working context in the laboratory.

Q: Who is the responsible person in GDP, and what do they carry? The responsible person is the named, suitably qualified individual who carries personal responsibility for a distributor's good distribution practice compliance: the quality system, the accuracy and completeness of records, staff training, approval of suppliers and customers, the handling of complaints, returns and recalls, and the conduct of self-inspections. The office exists so that distribution failures have a named owner, exactly as the study director owns a GLP study.

Q: What is the difference between an OOS and an OOT result? An out of specification (OOS) result falls outside the established specification and triggers the formal investigation procedure: a Phase I laboratory investigation for assignable laboratory error, then, if unexplained, a Phase II full scale investigation extending into manufacturing, with the quality unit deciding the batch's disposition. An out of trend (OOT) result is inside specification but against the expected pattern of results; it is a warning handled through trend review and monitoring, not through the OOS procedure, though a pattern of OOT results can justify raising an investigation of its own.

Q: What are the types of validation, and what is a Validation Master Plan? By timing, validation is prospective (completed before routine production, the modern default), concurrent (during routine production, in justified exceptional cases) or retrospective (from accumulated historical data on old stable processes, little accepted now). By object it covers processes, cleaning, analytical methods and computerised systems, built on qualification of premises, equipment and utilities. The Validation Master Plan is the site document that plans all of it: the inventory of systems and processes to be validated, the approach, responsibilities, documentation and schedule, and the revalidation policy.

Q: What are the four ICH guideline families, and what does the Q family contain? ICH files its harmonised guidelines as Q (quality), S (safety, the nonclinical family), E (efficacy, the clinical family, including E6 on good clinical practice) and M (multidisciplinary, including M4, the Common Technical Document). The Q family carries the quality system of this subject: Q1 stability, Q2 analytical validation, Q3 impurities, Q6 specifications, Q7 GMP for active pharmaceutical ingredients, Q8 pharmaceutical development and quality by design, Q9 quality risk management and Q10 the pharmaceutical quality system.

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