Guide to GAMP 5, data integrity and quality by design GxP manufacturing

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Contents

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What is a GxP manufacturing system?

Any computerized system controlling the manufacture of a GxP product, such as a pharmaceutical drug, is defined by the International Society for Pharmaceutical Engineering (ISPE) as a manufacturing system. A manufacturing system provides real-time control, collects and manipulates data, and typically offers a physical interface between systems, such as connecting a programmable logic controller (PLC) to your Distributed Control System (DCS). Above all, your manufacturing system should incorporate the FDA's principles of Quality by Design (QbD), as we'll see in this presentation.

ISA-95 Level 4
Enterprise planning and logistics functions; defines the business-related activities to manage a production organization
e.g. Enterprise Resource Planning (ERP) system

ISA-95 Level 3
Manufacturing operations management functions; defines the activities of the work flow to produce the desired end-products
e.g. Manufacturing Execution System (MES)

ISA-95 Level 2
Process control, supervisory control and data acquisition functions (batch, discrete or continuous process)
e.g. Process Control System (PCS)

ISA-95 Level 1
Sensing and Manipulating the Physical Process
e.g. individual sensors or actuators

ISA-95 Level 0
Physical Process

Manufacturing data
- Pressures, temperatures, etc
- Process modelling/multivariate analysis values

Manual inputs
- Action records
- Dispensing details

Integration data from other systems
- ERP data
- Manufacturing activity
- Other computerized systems

Manufacturing system

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Critical functions: how do we find them?

The FDA's Quality by Design (QbD) framework mandates robust product development underpinned by product and process understanding with clearly predefined quality objectives. ICH Q8 (R2) lays out a 4-step process for pinpointing and controlling the quality attributes and process parameters within your manufacturing system:

Process	Define Quality Target Product Profile (summary of desired quality characteristics)	Identify Critical Quality Attributes (CQA) of your manufactured product, and of any raw materials, ingredients or intermediates which feed into it	Determine how your critical material attributes (CMAs) and manufacturing critical process parameters (CPPs) impact these CQAs	Feed a corresponding control strategy into your manufacturing process, including: • Controlling input materials • Reviewing product specs • Controlling unit operations • Releasing and post-release monitoring
Example	Example QTPP on next slide	Content & blend uniformity	Particle size/distribution,load level and speed / duration of product mixer	Apply ranges of acceptable product output and manufacturing process execution with regular sample and test parameters for lab scale and exhibit batches

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Example quality target product profile (QTPP)

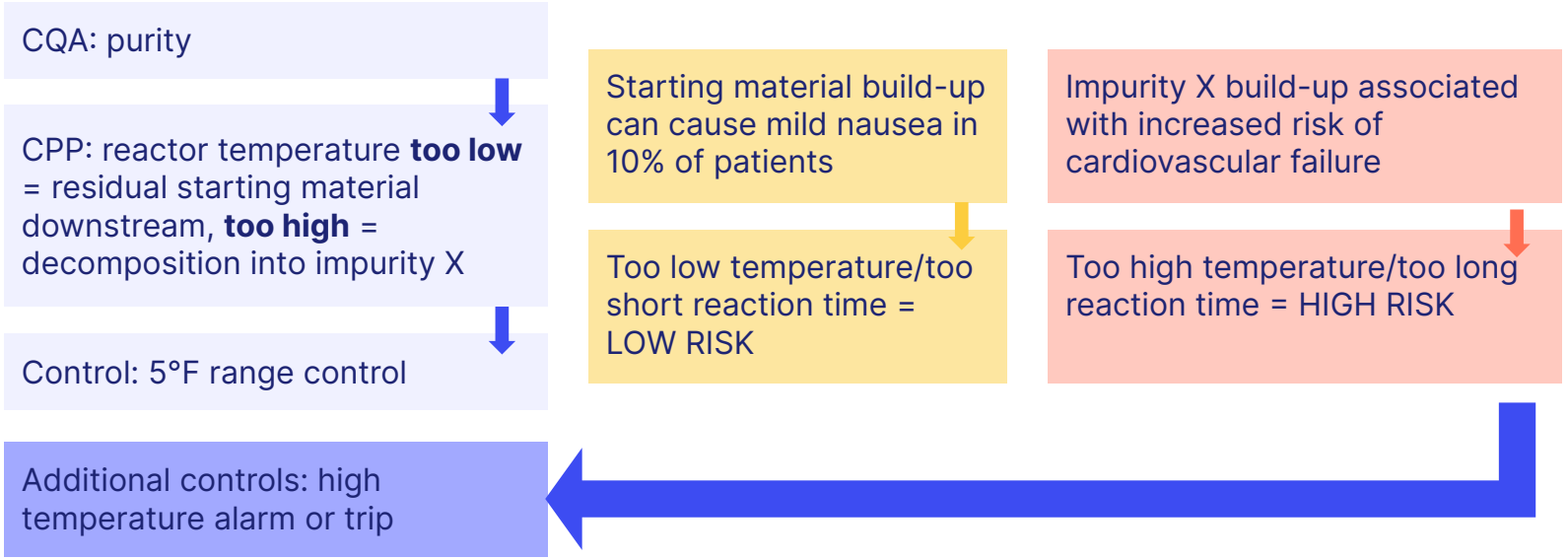
Source: FDA

QTPP Elements		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength		20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		Immediate release enabling T_{max} in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content Uniformity		
	Dissolution		
	Degradation Products		
	Residual Solvents		
	Water Content		
	Microbial Limits		
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and C_{max} by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

Risk management

Risks to **patient safety** and **product quality** should be identified, assessed and controlled throughout the Quality by Design (QbD) GxP manufacturing process.

Identifying high- and low-risk CQA and CPP combinations is crucial for an appropriate and measured control strategy. For example:



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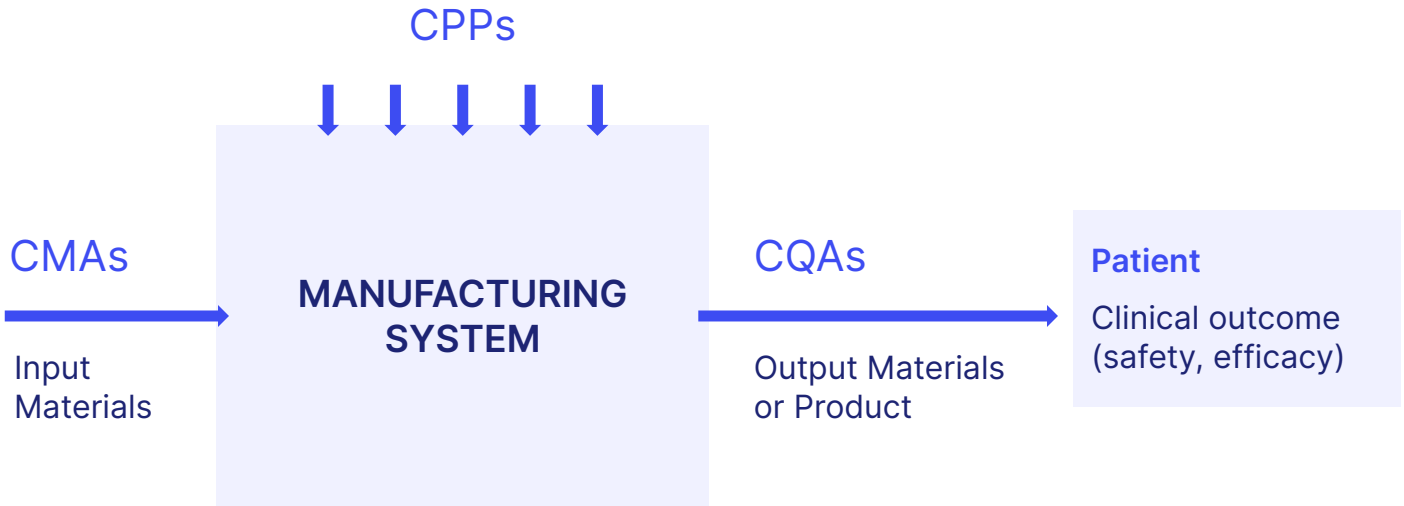
Remember...


CPPs
CMAs
Input Materials
MANUFACTURING SYSTEM
CQAs
Output Materials or Product
Patient
Clinical outcome (safety, efficacy)

Critical records: how do we find them?

Critical GxP records, in short, are the data underpinning the **control strategy** you devise in response to your identified CQAs, CMAs and CPPs. Examples include:

Control Strategy

Input Materials	Product Specification	Controls for Unity Operations	Release Strategy	Monitoring
Material management records, dispensing records, bill of materials	Batch details (reference, order details, expiry date), process values, audit trails, exceptions (alarm/event logs)	Equipment records, cleaning records, environmental records, SOPs, workflows, training requirements, configurations (security/access/backup controls)	Lab results, batch reports, release approvals, reconciliation records, methodology for batch release/reconciliation/audit trail reviews	Annual Product Reviews Handover process (GAMP 01) Maintenance/support processes (GAMP 02) Performance Monitoring process (GAMP 03) Incident Management process (GAMP 04) CAPA process (GAMP 05) Change Management and Configuration Management processes (GAMP 06) Repair process (GAMP 07) Periodic Review process (GAMP 08) Backup and Restore processes (GAMP 09) Business Continuity / Disaster Recovery processes (GAMP 010) Security Management processes (GAMP 011) System Administration process (GAMP 012) Retention, Archive, Retrieval processes (GAMP 013)

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Maximizing integrity of critical records and data

Your critical records naturally demand complete data integrity.
5 questions to ask yourself:

1. **What is the potential for patient harm if our data is inaccurate or patchy?**
2. **What are the main threats to the integrity of our manufacturing data?**
3. **How does data flow in the manufacturing process?**
4. **Where are the…**
    a. **Gaps?**
    b. **Areas of ambiguity?**
    c. **Areas of excessive data (noise)?**
    d. **Areas where full traceability and accuracy are threatened?**
5. **Where will we store and control our quality documents and data (paper, spreadsheets, eQMS)?**

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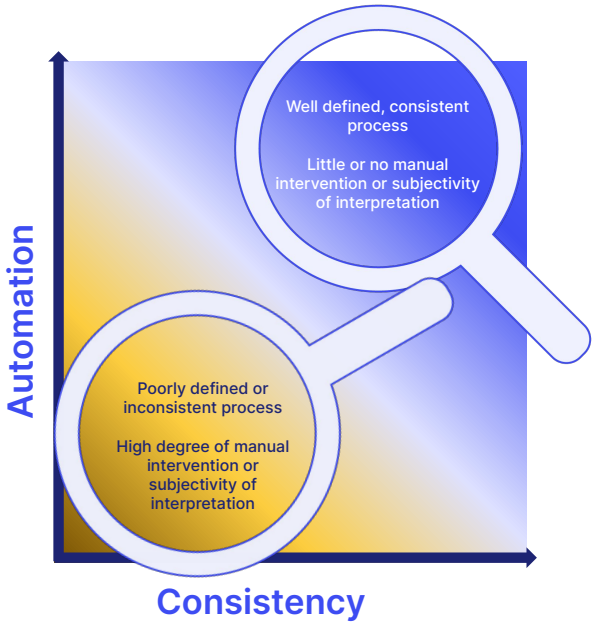
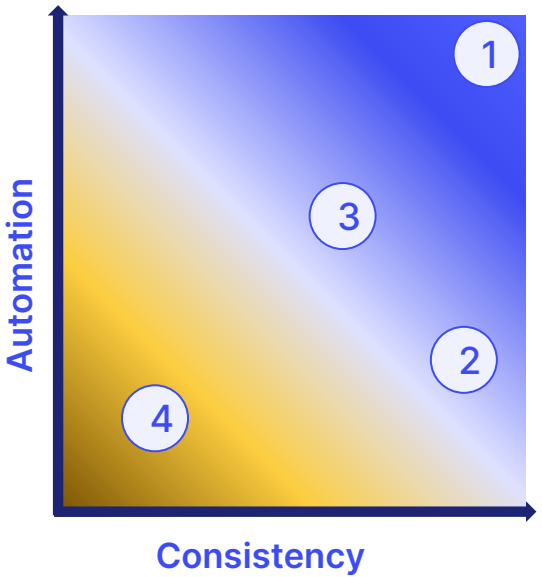
Good Manufacturing Practice vs. Bad



For example...



1. Thermocouple automatically capturing reactor temperature and reporting as pass/fail
2. Manual weighing of ingredients and input of weight data into control system
3. Vision recognition system checking packaging quality, with operator override in ambiguous cases
4. Manually stopping a tablet coating machine to achieve the right thickness

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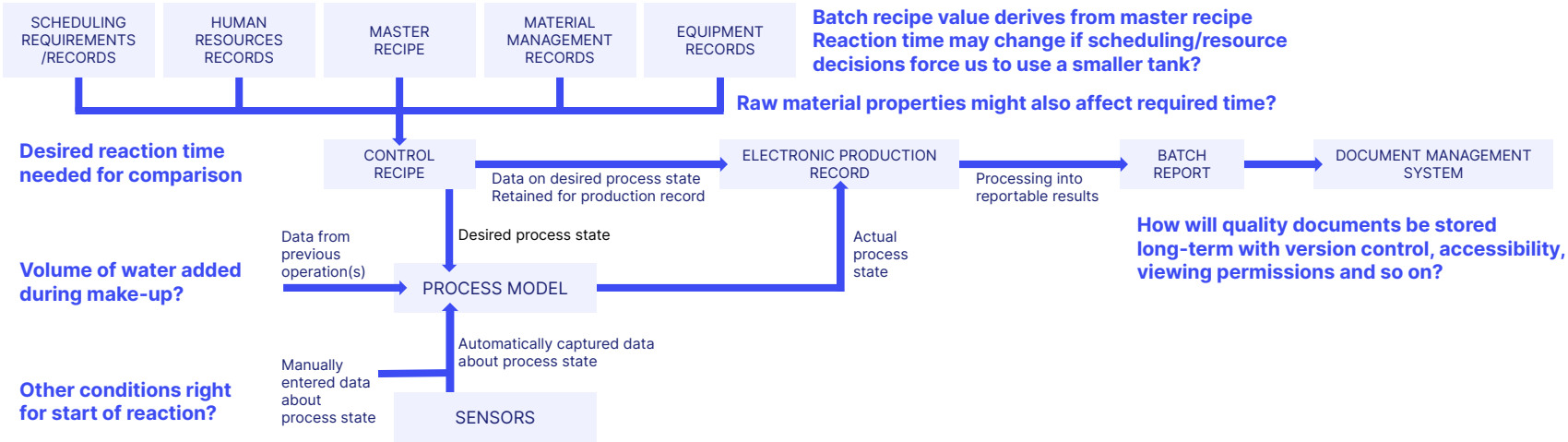
Understanding your data flows

To make accurate GxP quality decisions, you need batch reports driven by cogent, integrated data flows with managed risks and good documentation practice (GDocP). Consider the risks inherent to your current data and information flows:



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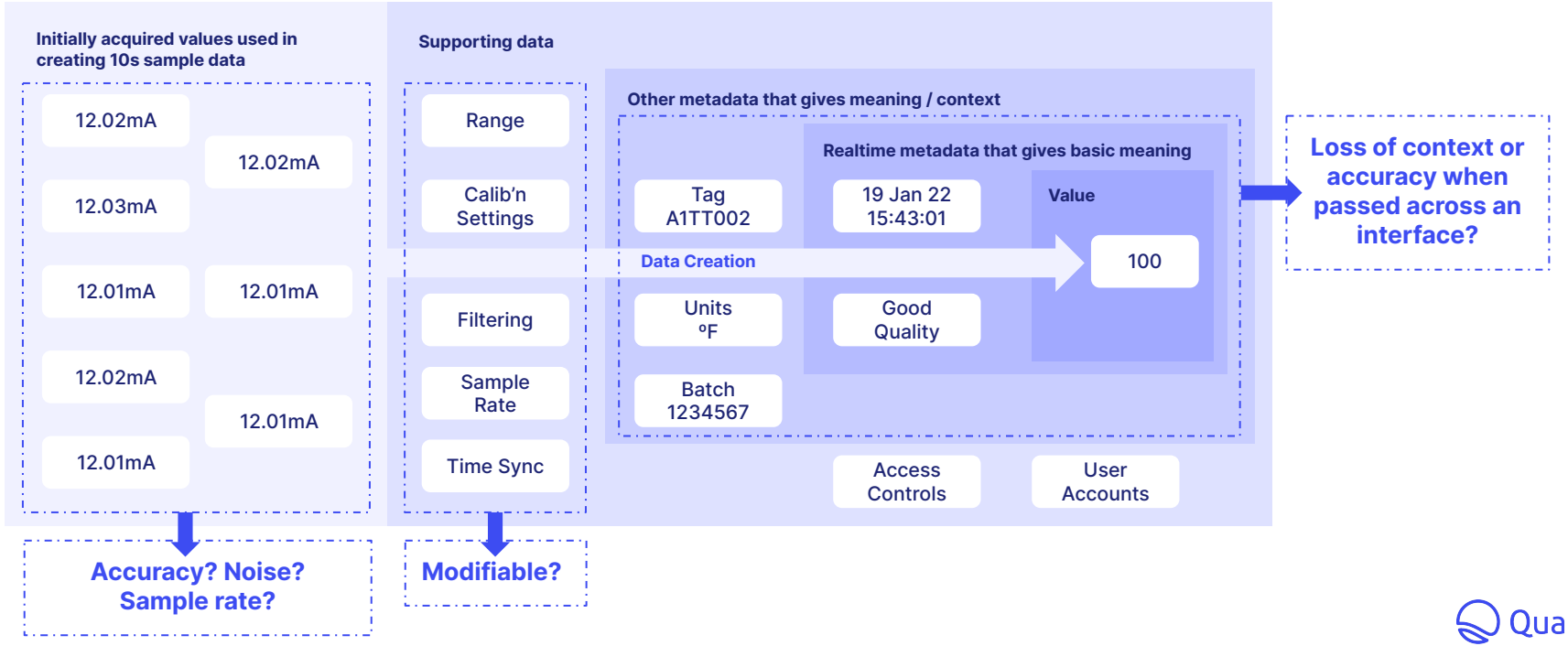
Understanding your manufacturing system

Even ‘simple’ areas of the manufacturing process like temperature capture invite risks to your data integrity, where values can be lost, altered or misconstrued. For instance:



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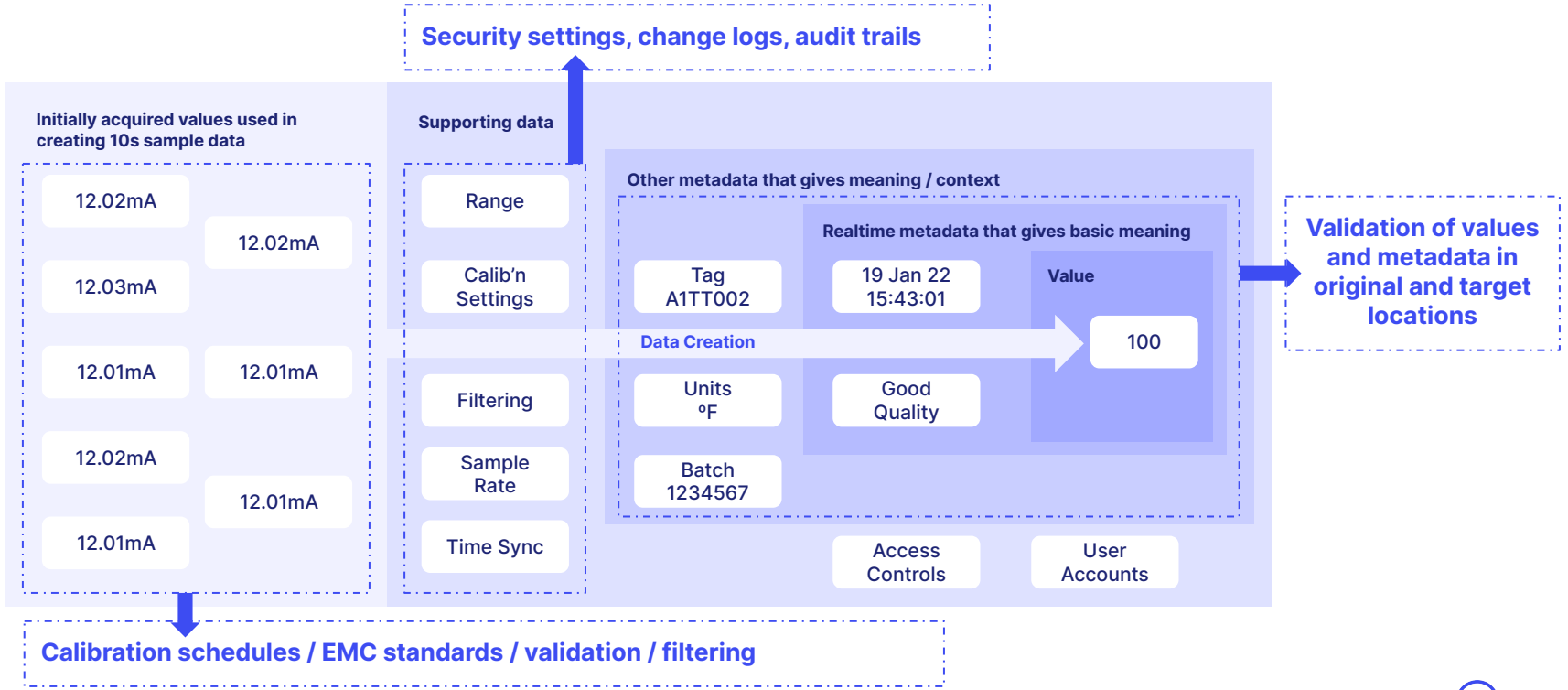
Strengthening your manufacturing system

Add controls, standards, filters and audit trails as appropriate:



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ALCOA+

ALCOA+ provides 9 data integrity benchmarks your GxP manufacturing system should incorporate:

Attributable:
To person (not applicable in this case but would be for a manual entry!)
To system (have we validated data path from sensor to batch report?)

Legible:
Correctly presented in human readable form for review?

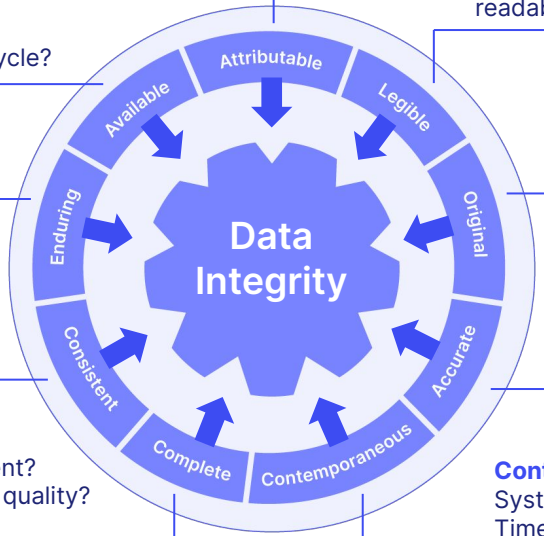
Available:
Retrievable throughout the lifecycle?

Original:
Metadata retained?
Reported value either protected or would include indication if it had been modified?

Enduring:
Recorded in a durable and maintainable form?

Accurate:
Sensor calibrated?
Reported value protected or would include indication if it had been modified?
Desired and actual values used correctly when deriving the pass/fail?

Consistent:
Timestamps consistent with rest of process sequence?
No unexpected events in audit trail?
No unauthorised changes to system?



Complete:
All required values present?
All required values good quality?
Metadata also retained?

Contemporaneous:
System time synchronises correctly?
Timestamps are correctly recorded?

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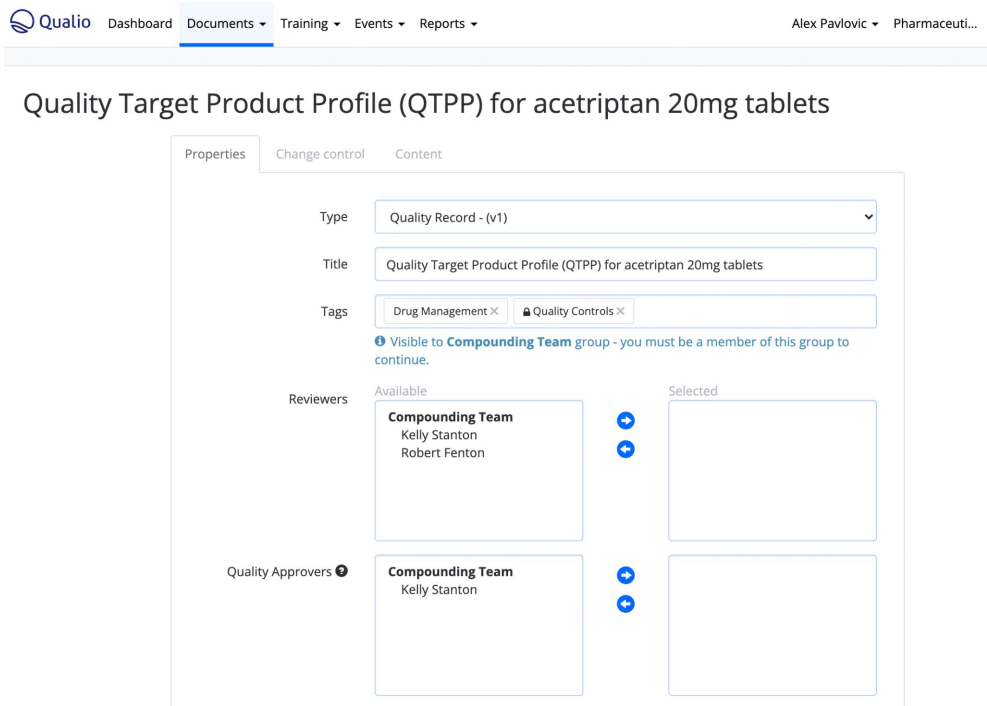
Controlling your GxP documents

A robust and modern GxP manufacturing quality system requires a considerable documentation stack:

- SOPs and policies
- Quality records (including CAPAs, internal inspection reports and change control)
- CSV documents (IQs, OQs and PQs) for computerized systems
- Training records
- Batch records
- Laboratory notes
- Bills of Materials (BOMs)
- Certificates of Analyses & Compliance (CoA/CoC)
- Logbooks
- Protocols
- Test methods
- Product/sample labels

Controlling your GxP documents

- Paper, spreadsheets and free legacy document management tools add extra risk to your GxP quality management system by compromising GDocP and ALCOA+ principles
- Consider how to embed GDocP and ALCOA+ into your document stack by investing in an electronic document management system with centralized access, version control, bespoke user permissions, incorruptible archiving and so on
- A robust manufacturing data flow should be underpinned by equally robust document management practices



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Applying Qualio for ALCOA+

Attributable: individual user actions fully time-stamped and audit-trailed

Legible: document templates encourage cogent, consistent records

Contemporaneous: superseded and outdated document versions automatically archived and replaced with the correct and current version

Original: All document versions maintained and accessible

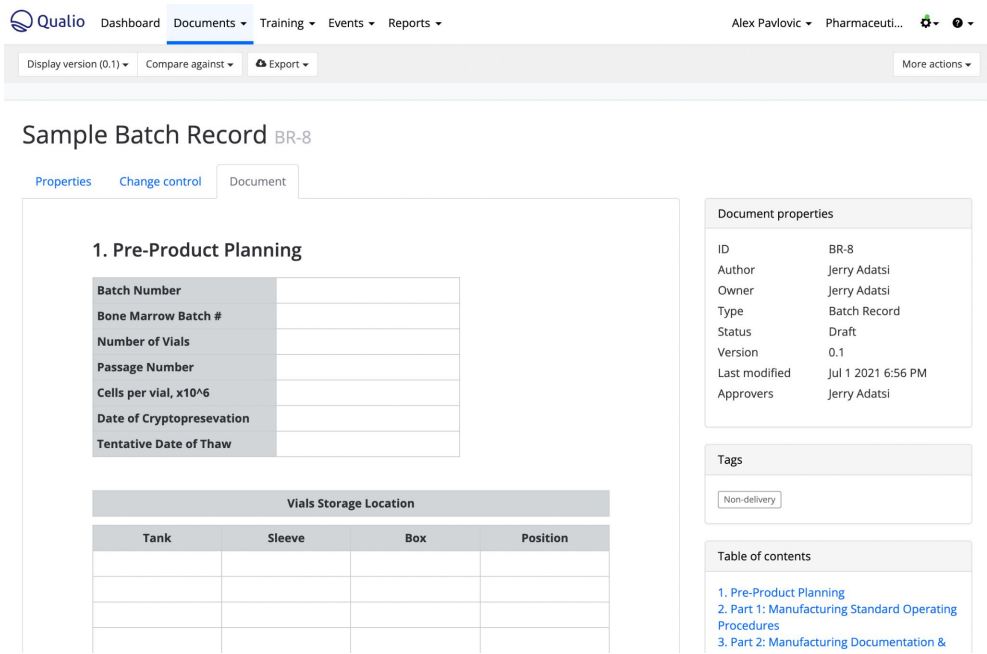
Accurate: review and approval workflows ensure only accurate information is made live and accessible

Complete: Qualio provides an incorruptible single source of truth where data is never deleted, only archived

Consistent: document templates and workflows enforce a consistent approach to drafting, review, creation, upload, and access

Enduring: cloud-based backups, audit trails, change logs and document archives provide a persistent and enduring document repository

Available: Qualio is accessible from anywhere in the world with just an Internet connection and secure user login, breaking down operational silos and connecting your teams to critical quality data



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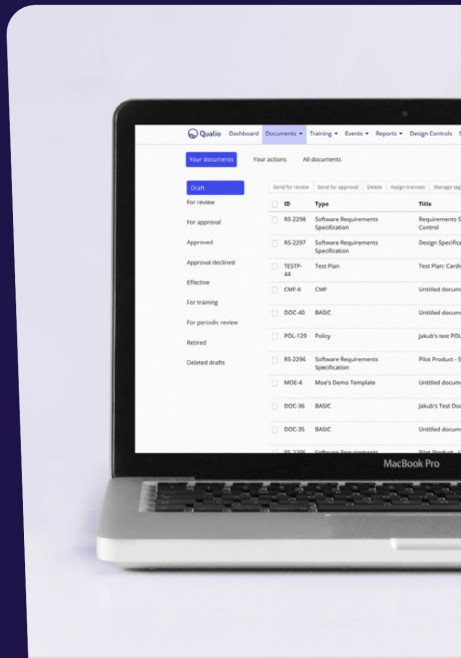
7 top tips

1. Begin with the end in mind to bake quality by design into your manufacturing process from Square 1
2. Ensure every identified CQA corresponds to material attributes and process parameters with an appropriate control strategy
3. cGMP is impossible without application of a GDocP and ALCOA+ methodology to your critical GxP records
4. Let patient safety be the guiding principle of your QTPP and CQAs
5. Measure risk to home in on the handful of CPPs and CMAs to prioritize your effort on
6. Apply ICH Q8 (R2) and the FDA's Process Analytical Technology (PAT) framework to your GAMP manufacturing system
7. Consider how to maximize automation and consistency at all stages of your quality activities by investing in appropriate quality management platforms and tools

See our GxP quality management software in action

qualio.com/demo



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