Qualification of GMP Equipment –
Supercritical Fluid Extractor

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Overview

Overview

In 25 minutes, what can we achieve?

Some specific things to look for with supercritical fluid extraction

In our experience, what are the some of the bigger challenges to successful qualification?

An overview of modern GMP lifecycle for equipment qualification

Concepts that can be applied to just about any GMP equipment

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Why do we need to qualify?

In Australia, for GMP licensing, compliance with PIC/S PE009 Annex 15 is required

> It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed.

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OK … Let's get qualifying!

Modern validation is much more than "test and forget".

Regulators have expectations that manufactures have deep understanding of both the "why" and the "how" of their processes

Why have you chosen this process or equipment?	Why is it the right solution for your final product?	How does your process work?	How did you determine what was important?

Prove to us that you have this detailed knowledge … before you start testing

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Where do we start?

GMPs now expect that manufacturers have a full understanding of their product CQAs to inform decisions on:

- Process optimisation
- Equipment selection
- Monitoring and recording requirements
- Quality decisions, such as non-conformance investigations

CQAs will generally be analogous to product specifications

CQAs that might be relevant in an SFE

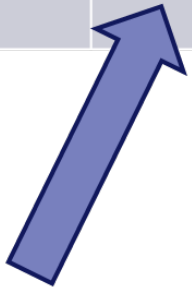
- Yield/ Recovery
- Cannabinoid Concentration
- Impurity levels
- Quality decisions, such as non-conformance investigations

Qualification risk assessment

In it's most basic form

- GMP product quality/patient safety risks only
- Not OHS or business risks
- Considers risks against process design

GMP Impact System	What GMP Risks Exist	Mitigations at DQ	Mitigations at IQ	Mitigations at OQ	Mitigations at PQ



Potentially significant effort here to minimise work at later stages

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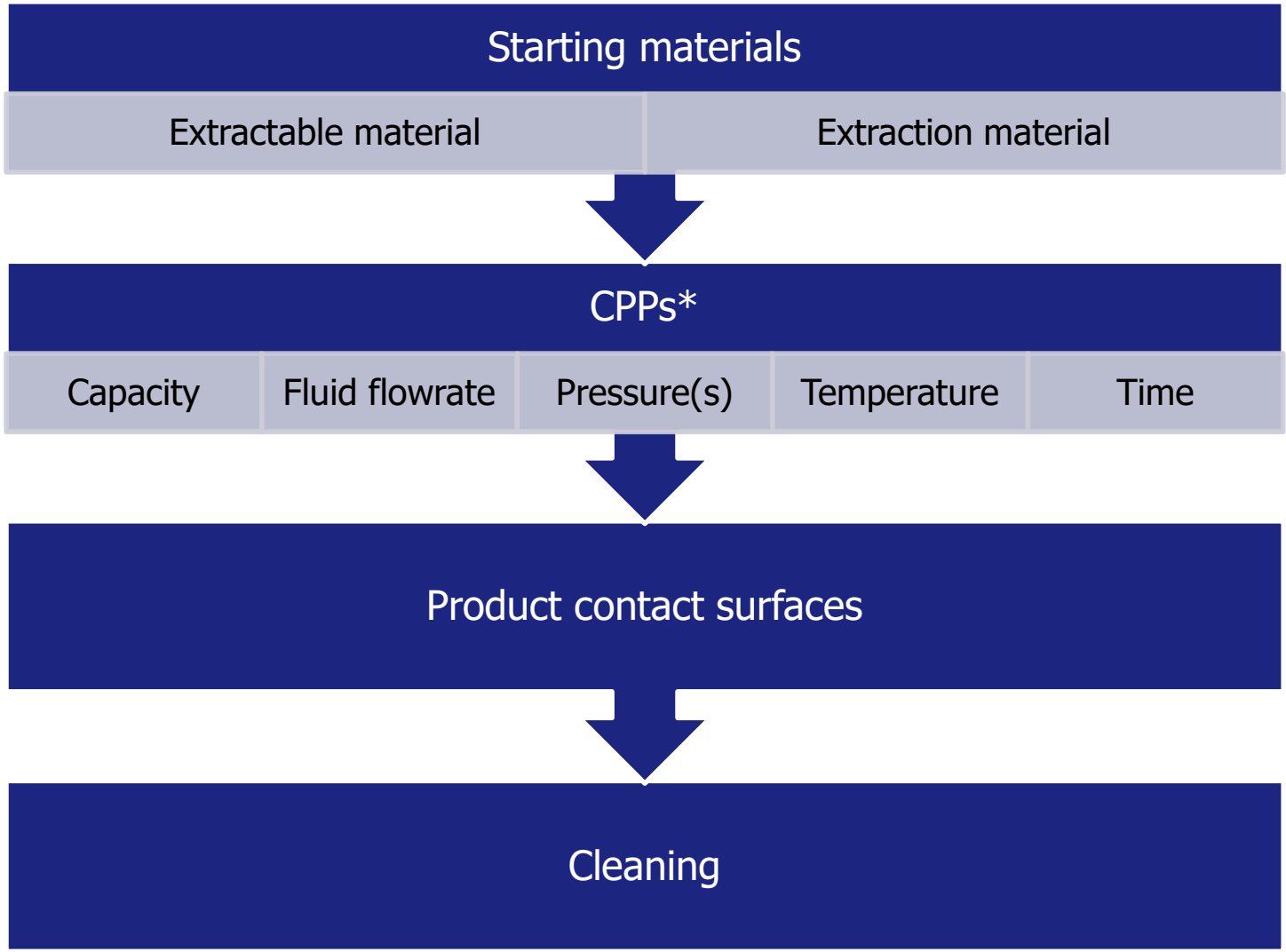
Some risk assessment considerations for SFE



*Understanding of CPPs should be targeted as early as possible

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Validation planning

All validation activities should be planned

VMP works at a site or large project level

Project plans are necessary for:

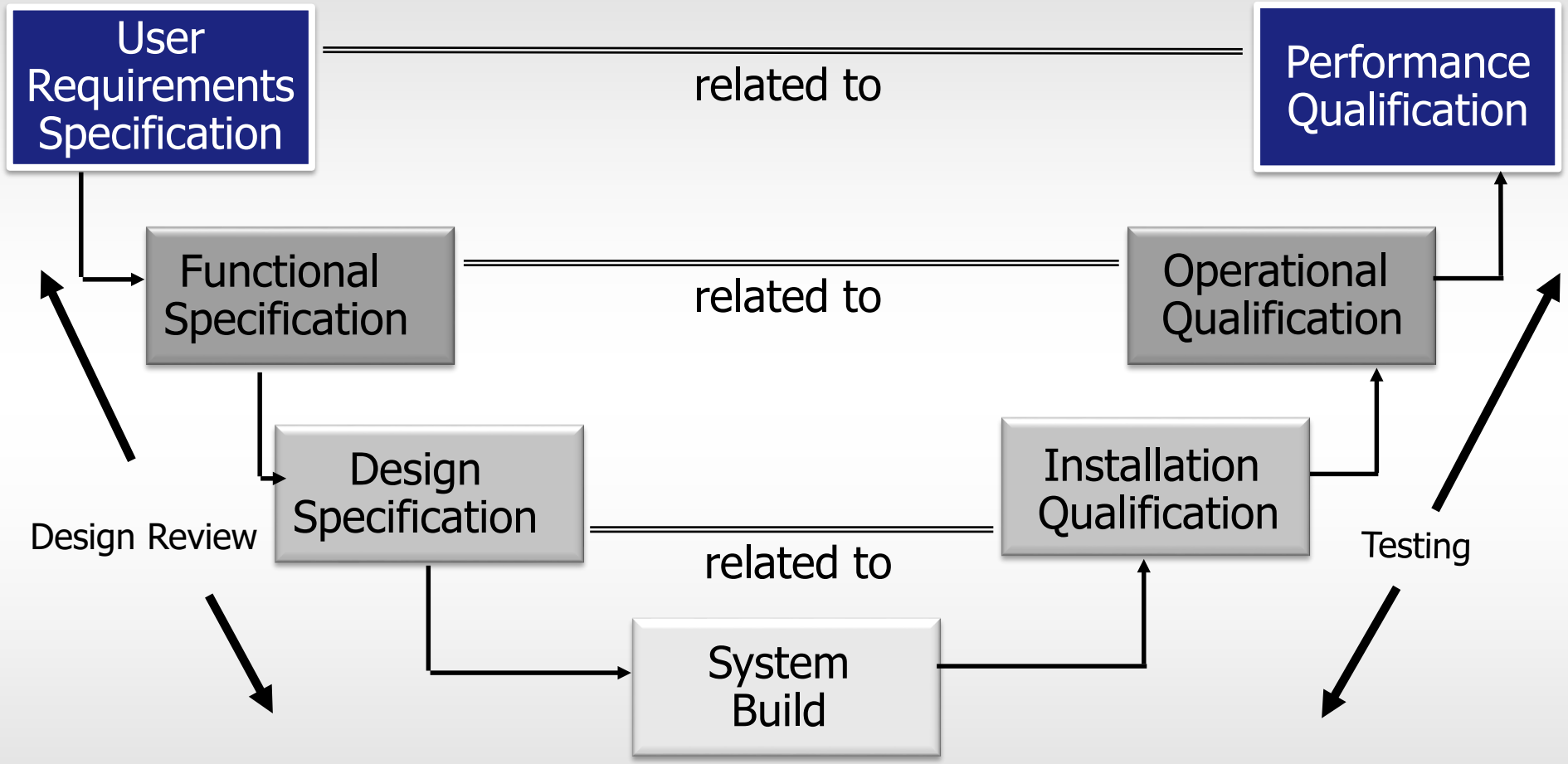
- smaller projects
- Sub-sections of large project VMPs

?

Validation planning

- System overview and scope
- Validation activities, deliverables and acceptance criteria
- Validation approach, strategies and rationales
- Quality risk management activities/outcomes
- Responsibilities
- Procedural and reporting requirements

Stage 2A – FS&E Qualification

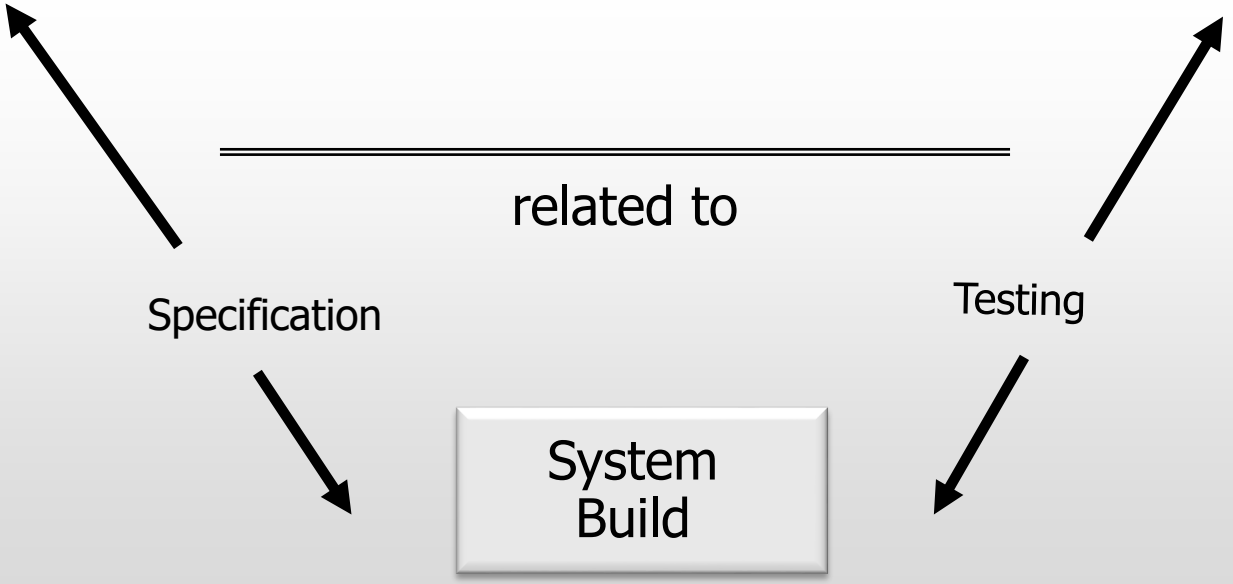


The Traditional 'V' Model

User requirement specification

ASTM E2500 (2007) inadvertently redefined V-model for non computerised systems

- General concept of **specification** "to communicate requirement inputs, including product quality considerations, to … design"
- Links specification to verification (testing) through the concept of "critical aspects" (specification should focus on critical aspects → verification should confirm …within acceptable limits.)
- Other guidance's have followed (notably ISPE)



URS basics – current status of URS

New Annex 15 (2015) specifically requires a URS (and/or FS) for all new FS&E and systems used in GMP manufacture

User requirements specification (URS)

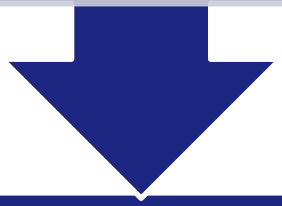
3.2. The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle.

- Essential elements of quality – GMP critical requirements
- GMP risks mitigated *prior* to URS writing
- Point of reference throughout lifecycle (living document)

User requirement specification

A URS defines GMP critical requirements for facilities, services, equipment and systems. It can be used to:

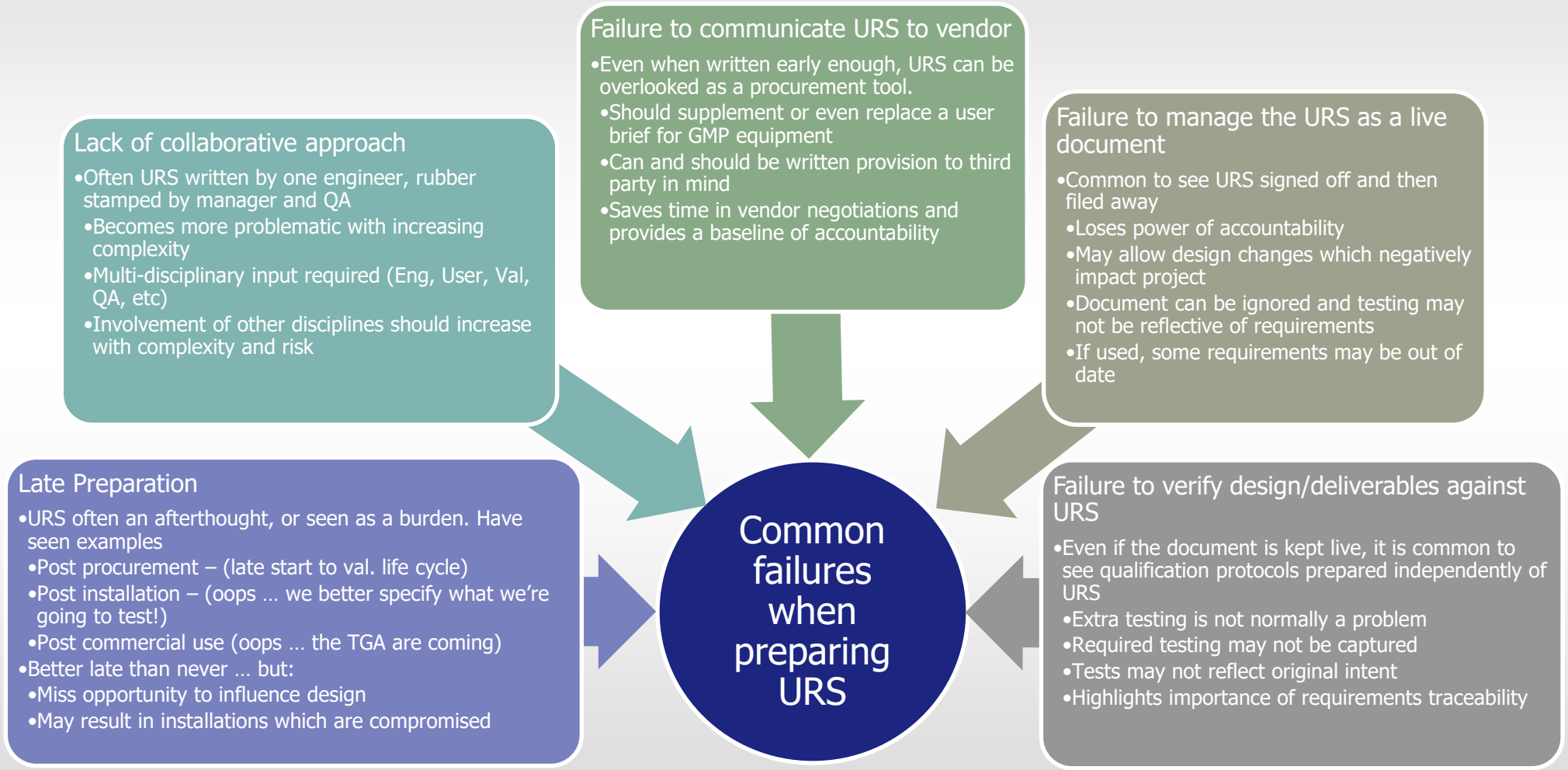
Define the requirements for an entire project	Define the requirements for a single piece of equipment	Support procurement



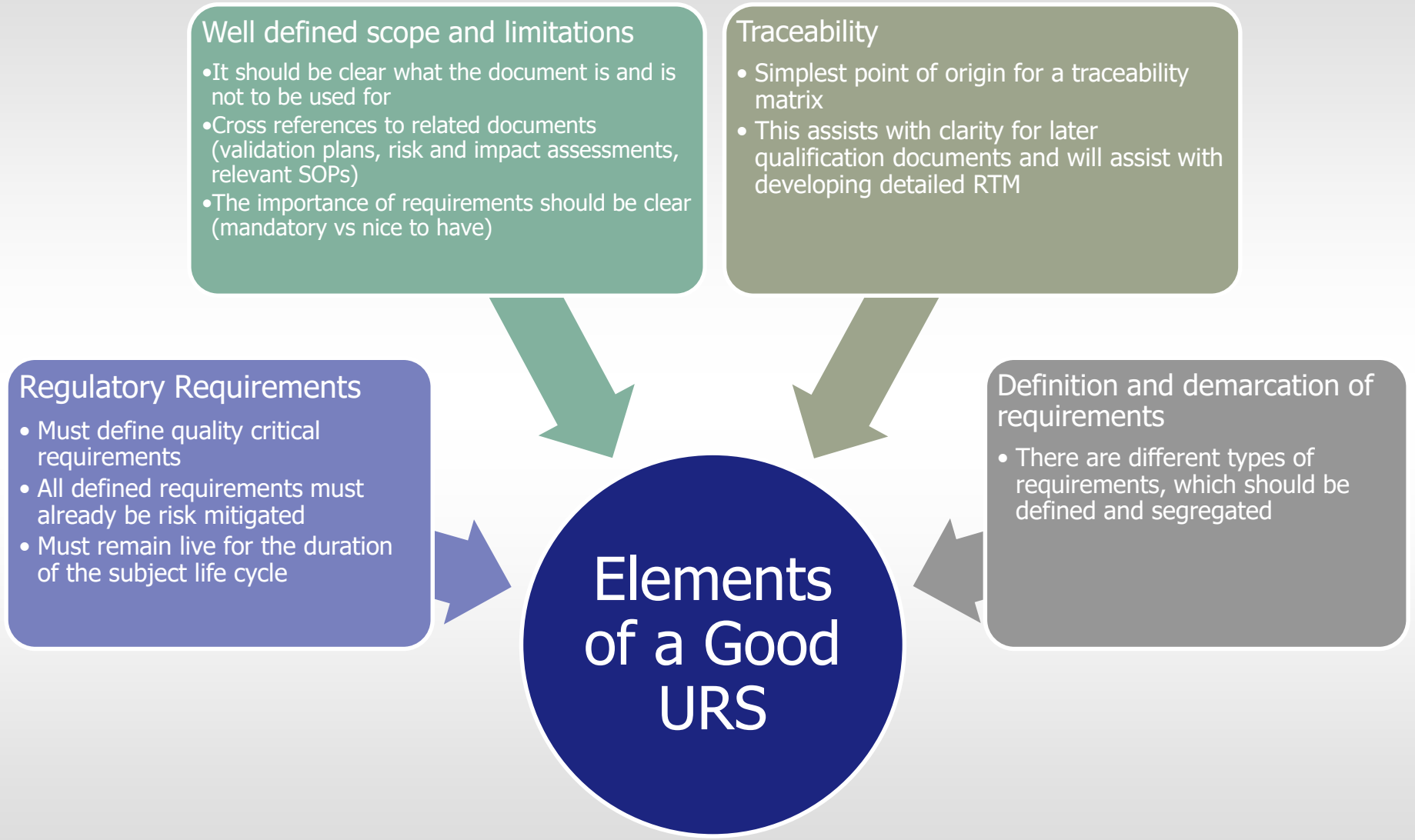
Not just for testing requirements

Also helps convey general GMP expectations which might not otherwise be testable	Provides a mechanism to hold vendors (and site personnel) to account

Common failings relating to URS documents



Elements of a Good URS



URS considerations for SFE

- Documentation requirements (quality)
- Documentation requirements (instructional)
- Vendor testing expectations (FAT/SAT)
- Finish quality standards (welds/materials)
- Yield expectations
- Recycling of extraction fluid (including quality expectations)
- Training

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Design Review/Qualification

To verify that the design of the system complies with GMP and the URS. Should verify:

- Design against URS (design review)
- Completion of necessary pre-installation activities where required, for example:
  - Risk and impact assessments
  - FAT (if required)
  - Functional and design specifications (if required)

FAT/SAT (Vendor Testing)

Effort will be dictated by:

Economics (how much is affordable)	Experience (how much do we already know in-house)	End product (API vs FDF likely to have different approach)

Vendor testing (to demonstrate compliance with specifications) is desirable to the extent practical to minimise qualification risks

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CPP finalisation

- You've got a working extractor … what then?
  - What confidence level do you have?

Consistent inputs → Stable process → Product meeting CQAs

Do you need to:	Perform further product/process development (improve confidence that process results in product meeting CQAs)
	Perform further engineering trials (improve confidence in reliability, operability and performance of equipment)

Installation Qualification Protocol

- Verification of previous stage completion
- Confirmation of correct installation of equipment
- Collation of supplier documentation.
- Documentation of calibration requirements (and current status).
- Verification of materials of construction, where GMP critical
- Preventative maintenance requirements
- Record of computerised systems
- Record of GMP critical components
- Record of GMP critical drawings (custom assemblies, P&IDs, facility layouts)
- Record of exceptions
- Phase acceptance and progression

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IQ for SFE – Expect challenges

Vendor supplied documentation!	
	Materials of construction
	Calibration certificates
	Calibration methodology
	Critical component documentation (e.g. valves)
	Operational instructions – especially cleaning
	Installation specific diagrams

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Operational Qualification

Tests developed from system knowledge (e.g. vendor, experience, development)

Tests should include "worst case" conditions or upper and lower operating limits

Subject material may not need to be justifiably representative

Operational Qualification Protocol

- Verification of previous stage completion
- Verification of GMP critical functionality (CPPs)
- Verification of GMP critical alarms (CPPs)
- Establishment of relevant QMS procedures
- Recording of training activities for the system
- Record of exceptions
- Phase acceptance and progression

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OQ for SFE – Expect challenges

Computerised Systems	Is the controlling software GMP compliant? (Annex 11)
	If not, what mitigations can be implemented?
Testing approach	What extractable material should be used if any?
	What are the acceptance criteria? – Software results based, independent? QC Analysis?
	Are you testing one set of parameters, or a range

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Performance Qualification

Tests based on process requirements → Tests should be representative of routine operation → Subject should be justifiably representative

Performance Qualification Protocol

- Verification of previous stage completion
- Perform using production materials or justified substitutes.
- Test should include range of routine parameters (CPPs) and assess measurable and relevant outcomes (CQAs)
- Should include interventions where appropriate
- Record of exceptions
- Phase completion and progression

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PQ for SFE – Less challenges

Defined process	Biggest challenge may be the starting material to be used
	If multiple routine conducted with different set point, the PQ may become complex
	If commercial material not used for PQ, correlation of acceptance criteria needs to be justified.
	Acceptance criteria, for the most part should be similar to product specifications

Validation Reporting

Each phase should be approved separately

Summary reporting should summarise results of each phase in a single source

Summary reporting should be a response to the plan and make a final disposition statement on the equipment

And finally - lifecycle management

Manufacturers expected to assess qualification status periodically

When do you re-qualify?

- Significant modifications or repairs (risk/criticality assessment)
- Change of CQAs and/or CPPs that isn't covered within existing qualification
- Trended data indicates shift (but only after corrective action)
- Other significant disruption to the equipment, such as physical relocation

But if equipment is operating as expected, no additional routine qualification testing is expected.

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