



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Validation and Qualification

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TGA Health Safety
Regulation

1. Annex 15 = reference point for GMP Auditors
2. QRM = flexibility to work smarter
3. Alternative approaches



Annex 15

Qualification and Validation



Annex 15 – Principle

“A risk assessment approach should be used to determine the scope and extent of validation”

- **Identify the validation work required**
- **Critical aspects requiring control**
- **Significant changes**
- **Plan and design the validation studies**

Use knowledge from R+D, pilots, scale-up

Require good knowledge of the process, equipment and product



Traditional Approach to PV

Equipment IQ,OQ,PQ or combination there of.

Keep in mind the objectives Annex 15 Clauses 12, 15 & 19

Process validation

- **Limited design and experimental studies**
- **Based on available information & manufacturing experiences**
- **Run 3 “golden batches” – clause 25**
- **Are all the objectives of validation achieved?**



(Enhanced)Traditional Approach to PV

PIC/S Post 2009 = beginnings of a life cycle approach ???

Continuous improvement over control of critical parameters and product

Includes:

- **Expect annual Product Quality Reviews – clause 1.4**
- **Revalidation and /or review – Annex 15:45**
- **Review and monitoring of QRM's – clause 1.5 & 1.6**
- **Ongoing stability studies - Clauses 6.23-6.33**
- **Effective and robust QMS- deviations, CAPA, change control, PM's etc**
- **Process capability mapping and monitoring, lean, 6 sigma**
- **Increasing implementation of PAT and real time release - overseas**



Possible Questions from auditors

What was validated?

What is controlled?

What is monitored?

What is the critical, non-critical, key and non-key variables?

What variables were considered, which ones impact on the process, which ones affect the product and to what degree?

How were variables controlled, monitored or validated?

How were acceptance criteria determined?

What are the conclusions? Are they supported with evidence?



2. Risk based approach



Annex 20 & ICH Q9 – Annex II

This Annex is voluntary

Annex II.6 – Quality Risk Management in Production: Validation

“To identify the scope and extent of verification, qualification and validation activities”

“To determine the extent for follow-up activities”

“To distinguish between critical and non-critical process steps to facilitate design of a validation study”



QRM and validation

Points to consider includes:

- 1. Need to relate the studies/approach back to code requirements**
- 2. Use of Validation Master Plan (Annex 15:4)**
 - Define the approach
 - Define any terms used such as control strategy, design space, PAT etc
- 3. Need to communicate the risk strategy to regulators**
- 4. Use of appropriate QRM methodology**
- 5. Basis for grouping – dosage form, equipment train, formulation types**
- 6. Sampling – representative & statistical significance**



QRM example

Through an effective risk assessment and risk mitigation, a manufacturer was able to support the manufacture of a “certain” products in a non-dedicated facility (3.6, 5.18)

1. Some of the specific points discussed were:

- **product protection strategy for the handling of different molecules.**
- **A clear understanding of campaign manufacture**
- **A team approach to risk assessment**
- **A process map to ensure all relevant factors are considered;**
- **The over-reliance on monitoring to support a position.**

2. Discussion with the regulator if significant deviation from expected and/or requires licence variations.

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Alternatives to traditional approaches



Challenges ahead

- **Incorporating Q8, Q9 and Q10 – EMA IWG 2011**
- **Are we ready for PAT & Real time release?**
- **Do we really understand our processes and products?**
- **FDA's 3 stage process validation guidance document – is this less or more work? Can it apply to existing products and processes?**
- **Are there other approaches to achieve the same goals?**
- **What is best for your organisation?**



The present & future?

Qualification and Validation is a code of GMP requirement

Process validation demonstrates the reproducibility of a process

Regulatory flexibility

Strong wish to facilitate technical innovation or the pursuit of excellence.

Trust building between regulators and industry

Common interest of protecting patients and public health

Goal - Processes are continuously verified as being capable of providing the desired product quality as an alternative to reliance on data generated from three production batches.



Fact check

cGMP PIC/S Jan 2009	Risk	Validation
Part 1	30	14
Part 2 - API	10	79
Annexes	379 mostly Annex 20	141 mostly Annex 15
Total	419	234



Questions (later)

- Interpretation of requirements
- gmp@tga.gov.au
- Auditors in Vic, NSW, ACT, SA, Qld