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National Validation Forum

by
Trevor Schoerie

Guidelines

- Please contribute
- Confidentiality – Chatham house rules
- Please network with other participants
- Please relax and enjoy yourself
- Phone on silent

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Objective

- Review current best thinking / practice
- Consistent national validation approach
  - For industry sector
  - Develop a framework
    - What, when and how
- Start of a journey, practical, value adding validation.

Why Commissioning and Qualification are Broken

Qualification for the 21st Century: A Proposal

Focus on unimportant engineering details

- No focus on critical components
- Design specs vs. submittals
- Nominal nameplate data
- IQ
- Design targets vs. requirements
- Target settings
- Valve sequences
- OQ
- Design targets vs. proper requirements
- PQ
- Design viewed as rigid specs; not as means of achieving requirements

Qualified systems that don't work

- Development batches
- Cycle development (CIP/SIP/Etc.)
- Start-up/ setting to work
- IQ/OQ/PQ too rigid for necessary testing
- Lack of requirements
- Poor team communication
- Lack of effective design review/ DQ
- Poor construction quality control
- Lack of GEP
- Lack of Proj. Chg. Mgmt.
- Three tries and we're done
- Troubleshooting subordina to clean documentation

Excessive Ti and Money

Fear of regulatory action

- Inconsistent interpretation by regulators
- ISPE Guidelines not universally accepted/ respected
- Not defined: what is NOT required
- Risk-based approach not well understood

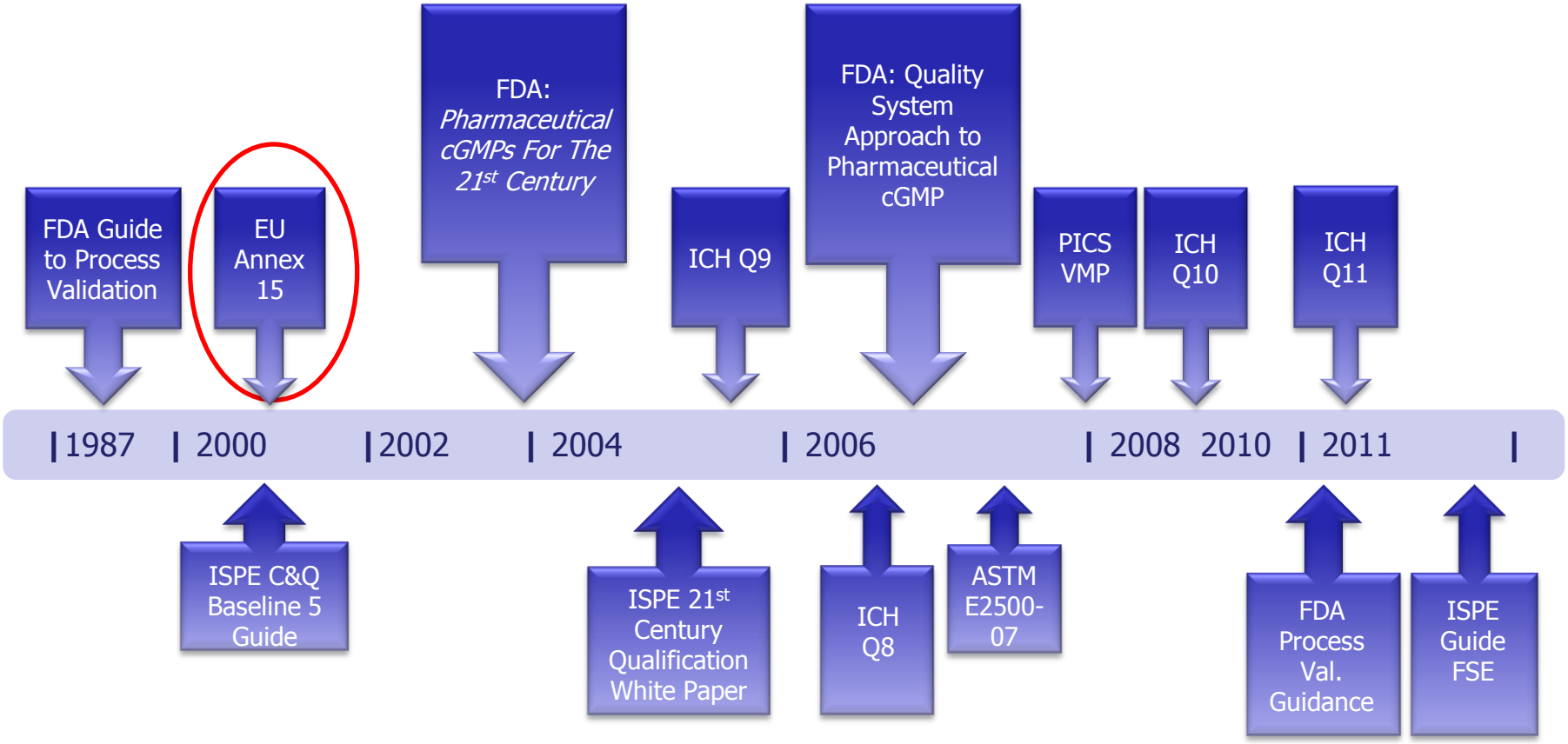
Process "rules"

- Doc approval bottlenecks
- QA approval of everything
- Word-smithing of trivial issues
- All issues have equal weight
- Pre-mature use of QA pre-approved CC
- Restrictive sequencing of activities
- Non-value added good doc. practices
- Discarding valid GEP evidence of conformance
- Onerous deviation procedure

Thanks to ISPE

NOTES:
1. Not all firms are hampered to the same degree or by all factors.
2. C&Q Baseline Guide addresses many of these issues; not universally accepted.
3. Qualification of PAT systems may require further engineering flexibility and focus of QA on science

Influences on validation



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Australian GMPs - Risk

Year	GMP reference	x times risk mentioned
1971	First TGA code of GMP	3
1990	TGA GMP code (Blue Book)	20
2002	First PIC/S code adopted in Australia	57
2009	Current – 2009 version of the PIC/S GMP code	**390**

ICH	ICH Title	x times risk mentioned
Q8	Pharmaceutical Development (2006)	10
Q9	Quality Risk Management (June 2006)	279
Q10	Pharmaceutical Quality System (April 2009)	34
Q11	Development & Manufacture of Drug Substances (4/2011)	51

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Progress - Process

- Stage 1 (past 6 weeks)
  - Developed concepts / Examples
- Stage 2 (today and tomorrow)
  - Develop common understanding
    - » Industry sectors / dosage
    - » Risk/CQA/CPP
    - » Control Strategy
    - » Commissioning, verification & qualification
  - Workshop issues
  - Q&A
- Stage 3 (next two years)
  - Develop a national guideline

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PIC/S Definition

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 009-9 (Intro)
1 September 2009

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS

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PIC/S Definition

"25. Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions.

In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation.

It is generally considered acceptable that **three consecutive batches/runs** within the finally agreed **parameters**, would constitute a **validation of the process**."

2009 PIC/S Guide to Good Manufacturing Practice for Medicinal Products – Annex 15

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PIC/S Definition

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 006-3
25 September 2007

RECOMMENDATIONS

ON

VALIDATION MASTER PLAN
INSTALLATION AND OPERATIONAL QUALIFICATION
NON-STERILE PROCESS VALIDATION
CLEANING VALIDATION

PH 1/96 "Principles of Qualification and Validation in Pharmaceutical Manufacture"

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PIC/S Definition (Recom. VMP)

Critical Operating Parameters / Critical variables

*"It is a requirement of GMP that each pharmaceutical company identifies what qualification and validation work is required to prove control of the **critical aspects** of their particular operation. **Common sense** and an **understanding of pharmaceutical processing** go a long way towards determining what aspects of an **operation are critical.**"*

*"...encompassing **upper and lower processing** or **operating limits** and **circumstances**; commonly referred to as "worst case" conditions."*

RECOMMENDATIONS ON VALIDATION MASTER PLAN…. 25th September '07

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FDA Process Validation (Enhanced validation)

Guidance for Industry

Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

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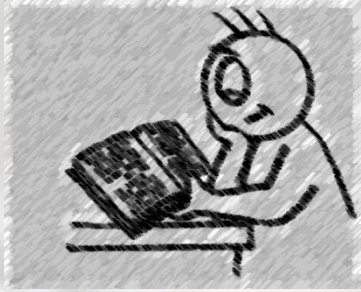
Process Validation
FDA Definition



"**Process Validation** requires documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

*[FDA Guideline General [FDA Guideline General Principles of Process Validation, **May 1987**]*

"**Process Validation** is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the **lifecycle** of the product and process. This guidance describes process validation activities in **three stages**.

*[FDA Guidance for Industry Process Validation: General Principles and Practices, **Jan 2011**]*

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FDA Definition

Stage 1 – **Process Design**: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – **Process Qualification**: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – **Continued Process Verification**: Ongoing assurance is gained during routine production that the process remains in a state of control.

[FDA Guidance for Industry Process Validation: General Principles and Practices, Jan 2011]

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FDA Definition

The terms ***attribute**(s)* (e.g., quality, product, component) and ***parameter**(s)* (e.g., process, operating, and equipment) are not categorized with respect to ***criticality*** in this guidance. With a lifecycle approach to process validation that employs risk based decision making throughout that **lifecycle**, the perception of **criticality as a continuum rather than a binary state is more useful**.

[FDA Guidance for Industry Process Validation: General Principles and Practices, Jan 2011]

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Industry sectors / dosage

- Route of administration
  - Parenteral (all injections and infusions)
  - Inhalation (nasal and oral)
  - Ocular (eyes)
  - Transdermal (absorption through the skin)
  - Oral (digestive/buccal/sublabial/sublingual)
  - Rectal/Urogenital (pessaries/suppositories)
  - Otologic (ears)
  - Dermal (topical)
- Therapeutic effect
- Toxicity / Allergenic/Sensitising effect
- Method of Manufacture
- Regulatory requirements/constraints

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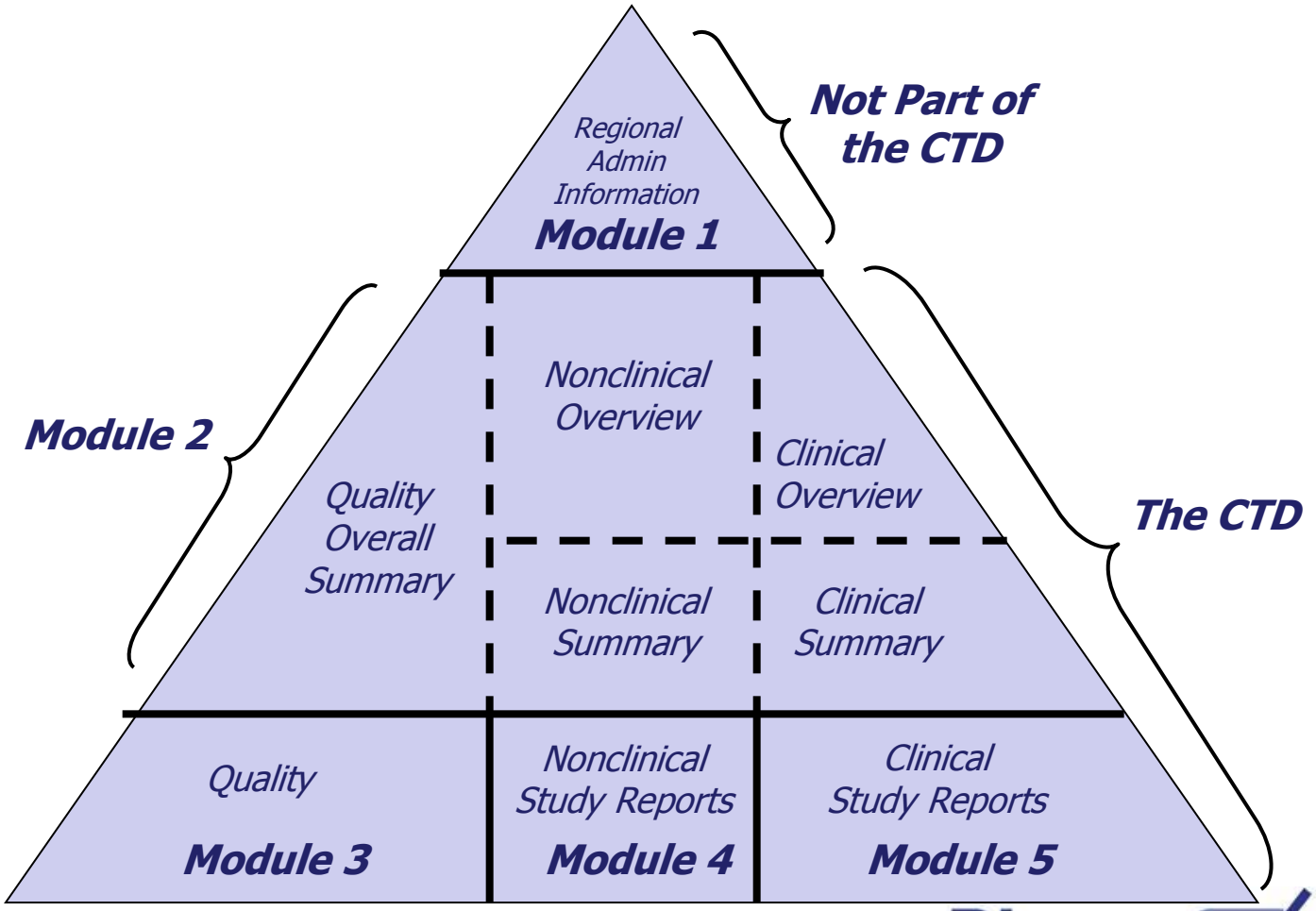
Type of Control → Drug Substance CQA (3.2.S.2.6) / Limit in Drug Substance↓	In process Controls (including In-process testing and process parameters)	Controls on material attributes (raw materials/starting materials /intermediates)	Impact of Manufacturing Process Design	Is CQA tested on drug substance/ included in Drug Substance specification (3.2.S.4.1)
Organic Purity				
Impurity X NMT 0.15%	Design space of the reflux unit operation composed of a combination of %water in Intermediate E and the reflux time in step 5 that delivers Intermediate F with Hydrolysis Impurity ≤0.30% (3.2.S.2.2)			Yes/Yes
Impurity Y NMT 0.20%	Process parameters step 4 (3.2.S.2.2) $p(H_2)$ ≥2 barg T <50°C In-process test step 4 (3.2.S.2.4) Impurity Y ≤0.50%			Yes/Yes
Any individual unspecified impurity NMT 0.10%		Specs for starting material D (3.2.S.2.3)		Yes/Yes

Common Technical Document (CTD) - Quality (ICH M4Q) guideline



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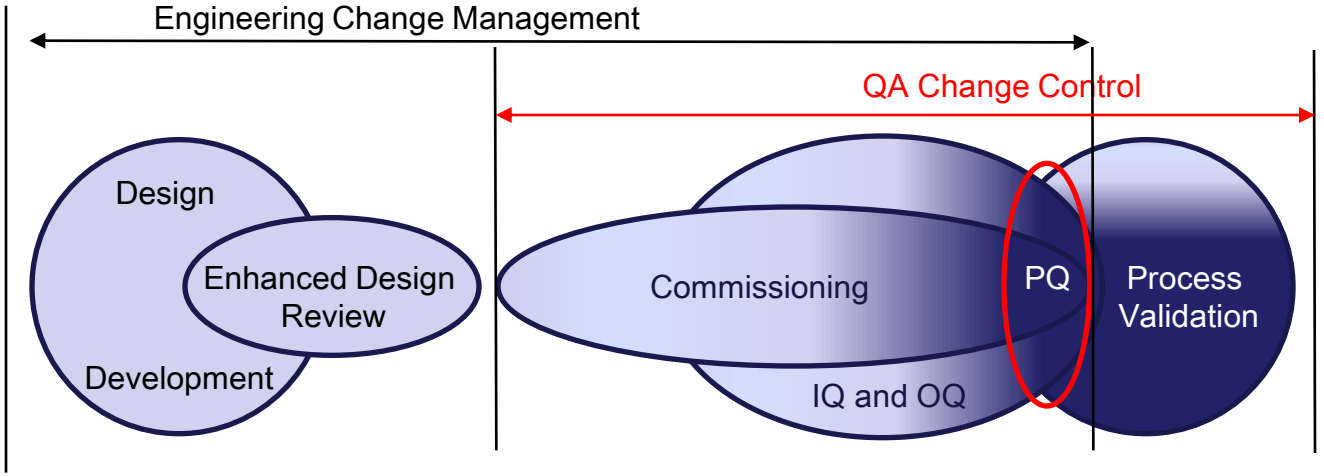
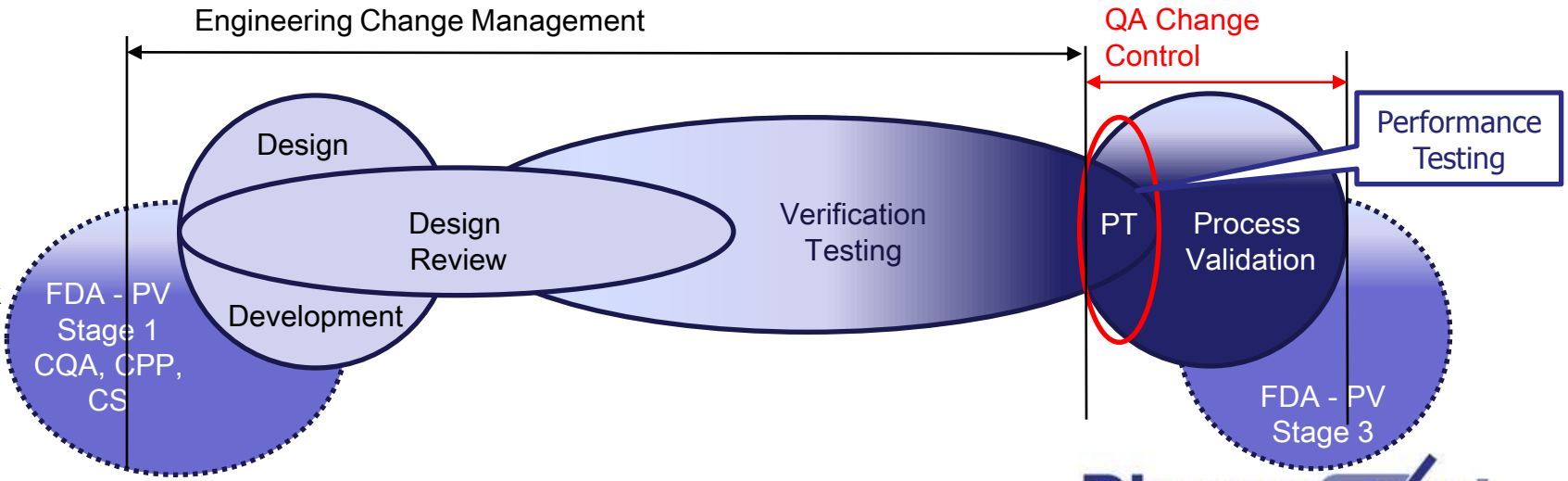
Commissioning – verification – qualification debate

Traditional approach – ISPE Baseline® Guidance 5



FDA – Risk based approach



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Thanks

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