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Benefits of using ASTM E 2500-07 a practical risk based & science based approach to validation

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What is ASTM E 2500

ÃñA **risk-based** and **science-based** approach to the **specification**,

design and verification of manufacturing systems and equipment

that have the potential to affect product **quality** and patient **safety**ò.

- Approved in USA in June, 2007
- It has a legal relevance
- Guidance was to develop a consensus approach

What is ASTM E 2500 (Contd.)

- Uses **Subject Matter Experts**
- Replaces sequential Commissioning and **Qualification** with ñ**Verification**ò
- Leverages **Vendors knowledge** and **documentation**
- Reducing the risk of **inferior quality** from Equipment Manufacturers
- Includes continuous process improvements and real-time monitoring (**PAT**)
- Not bound by the **formal** IQ, OQ PQ phases
- IQ, OQ, DQ, PQ are industry terms, **not FDA mandated**

What is ASTM E 2500 (Contd.)

- Replaces ñ**Qualification**ò with ñ**Verification**ò
- **Verification** – The act of confirming through objective evidence that a particular specification has been met.
- Verification is a systematic approach to verify that the systemsé are fit for intended useé
- ISPE has developed a new baseline guide Volume-12 : ñ**Science and Risk based approach for the delivery of facility, systems and equipment which will provide details on how to implement a program based on ASTM E 2500**ò

Current Qualifications

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Issues :

- Costlier
- Time consuming, leads to delay in launches
- Undue repetitions
- Regulation does not define how the qualification should be done
- Chosen to avoid all ill perceived risks
- Often the Qualified systems via formal protocols did not work correctly or consistently
- Without understanding manufacturing process may not lead to adequate assurance of quality

Current Qualifications (Contd.)

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Issues (Contd.) :

- Based on ó**anything can happen**ôphilosophy
- Qualifications are **not flexible** to accommodate required improvements, does not support **PAT** initiatives
- **Not process oriented** and do not have **experts** review mandated
- Any body can be on Qualification **without proper knowledge** and analytical tools
- The **Quality Assurance** team **may not have all experts** in their team to do the reviews and approval

Current Documentation

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Issues :

- Does not always add value
- Distracts effectiveness
- Self created practices due to lack of understanding on intent of GMP
- More focused on **Risk avoidance** ñSome one may askò, ñRegulators may demand itò, ñEnhance documentationò
- There is **no allowances for learning**, adjustments or changes to Functional Design during start up

cGMP Requirements

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Intends to Confirm, if the Equipment or the System :

- Properly installed
- Operate properly
- Meet the process requirements
- Control risk to product quality
- Support process validation

Expected Benefits

- Elevate our industry to more **knowledge**, better **understanding** of our manufacturing systems (**QbD**)
- Better technical understanding (**Subject Matter Experts**)
- **Less waste & repetition** (Expunge many of the non value added qualification practices of today)
- Focus on whatôs **important** (Critical) - More is not better
- Streamlines Process
- Reduces Cost & Time (**Use Vendor Documents**)

Expected Benefits (Contd.)

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- Separates GMP requirements from "**folklore**" qualification practices and expectations invented by ourselves in last 2 decades to avoid regulatory risks
- Design and implement better, more effective ways of ensuring our facilities, equipment, systems and associated automation are delivered in an efficient manner using **Good Engineering Practices**
- The **extent of verification** and the **level of detail** of documentation should be **based on risk**, including those associated with product **quality** and **patient safety**, the **complexity** and the **novelty** of manufacturing system

Expected Benefits (Contd.)

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- The standard provides **much latitude** as to how the various provisions of the standard are met
- The evaluations of the risk and performance is done by **SME** and focus towards process orientation
- **Pre-Commercial** changes can be done by use of appropriate SME with notification to Quality Unit for **critical aspects only**
- Significantly **shifts** current **Qualification** responsibilities to **Corporate Engineering Group**

Who have already implemented

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- **Amgen**

  Qualification of new manufacturing facility in Puerto Rico

  50-70% reduction in IQ/OQ for chromatography skid

- **Genentech**

  "Reduce repetition of testing", K Watters, ISPE Washington, 2010

  Christa Hartmann, Genentech, ISPE Tampa Meeting, 2009,

  "50% reduction in qualification testingò

- **Pfizer Global Engineering, ISPE Washington 2010**

  "80% reduction in # pages in validationò

Who have already implemented (Contd.)

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- **Bristol-Myers Squibb Biologics**

  "Applying ASTM E2500 to a Greenfield Site", E Bramhall, ISPE 2009

- **Pfizer**

  "Less duplication of testing and documentation", D Selby, ISPE Washington, 2010

- **Hyde Client, Commercial Device Manufacturer**

  E2500 for new Drug Device facility qualification

- **Integrity Bio systems**

  E2500 for WFI water system qualification

Comparison

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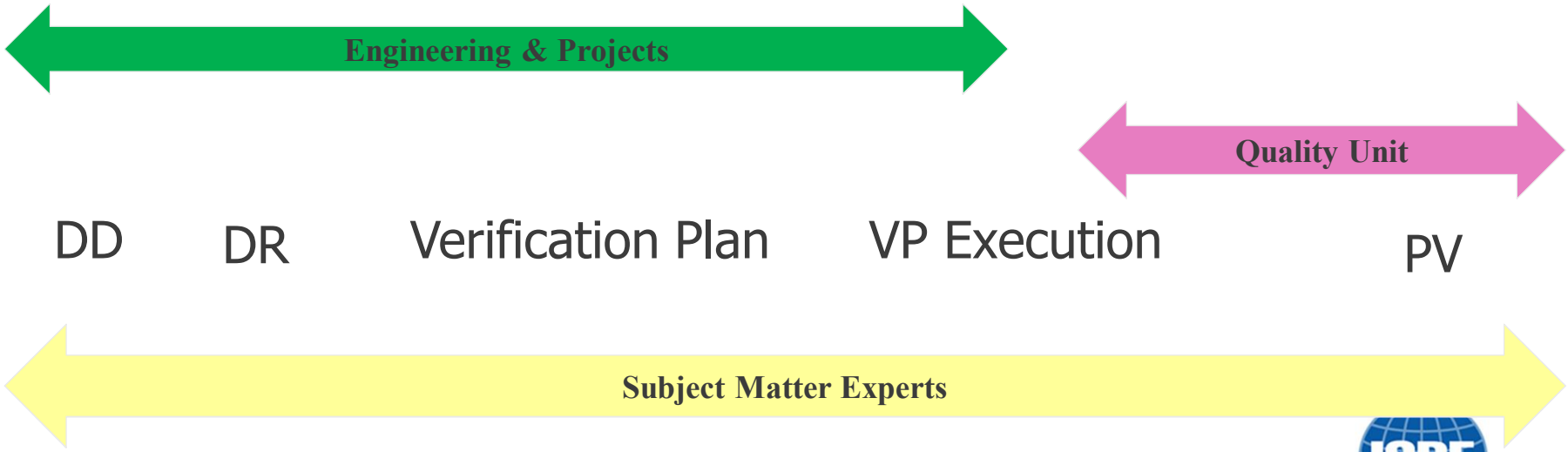
Current

Proposed



Comparison with Classic Approach

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Unchanged **Merged**

Activities	Classic Approach	ASTM Approach
Design basis / URB		
Purchased Order + User Requirement Specification (signed)		Purchase Order + Design Specification
Validation Master Plan		Verification Master Plan
User Requirement Specification	URS	Design specification
Functional / Design / Software / Hardware Specification	FDS	
Design Reviews & Vendor Agreement	DR	
Design Qualification	DS	
Verification Test Plan	IQ & OQ Protocols and Reports	VTP
Engineering Change Management	Project Change Management with different approvals	Specific approvals with SMEôs and QA on need basis

Comparison with Classic Approach (Contd.)

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Merged | **Additional in ASTM**

Activities	Classic Approach	ASTM Approach
Factory Acceptance Test	FAT, Protocol and Report	
Receipt Verification	In IQ	Verification Test
Commissioning		
Site Acceptance Test		
Installation & Operational Qualification Protocol	IOQ Protocol	
Installation & Operational Qualification Report	IOQ Report	
Discrepancy Management	Deviations	VTP
Performance Qualification		Verification Test
Risk Assessment *		Part of VTP
Requirement Traceability Matrix		
Turn Over Package		

*Using CPP, CQA & CS to arrive at Verification Test Plan

Comparison with Classic Approach (Contd.)

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Additionally the following has been done in the new concept:

- Use of approved vendor documentation to avoid unwanted repetition
- Involvement of SME(s) to improve the understanding of the process and bring more focus with proper risk assessment
- Use of Engineering Group for the qualification in their specific expertise areas
- The sequence of the activities is more science based than ritualistic
- Use of SME(s) to approve the changes which has no impact on quality related specifications

ASTM Workflow

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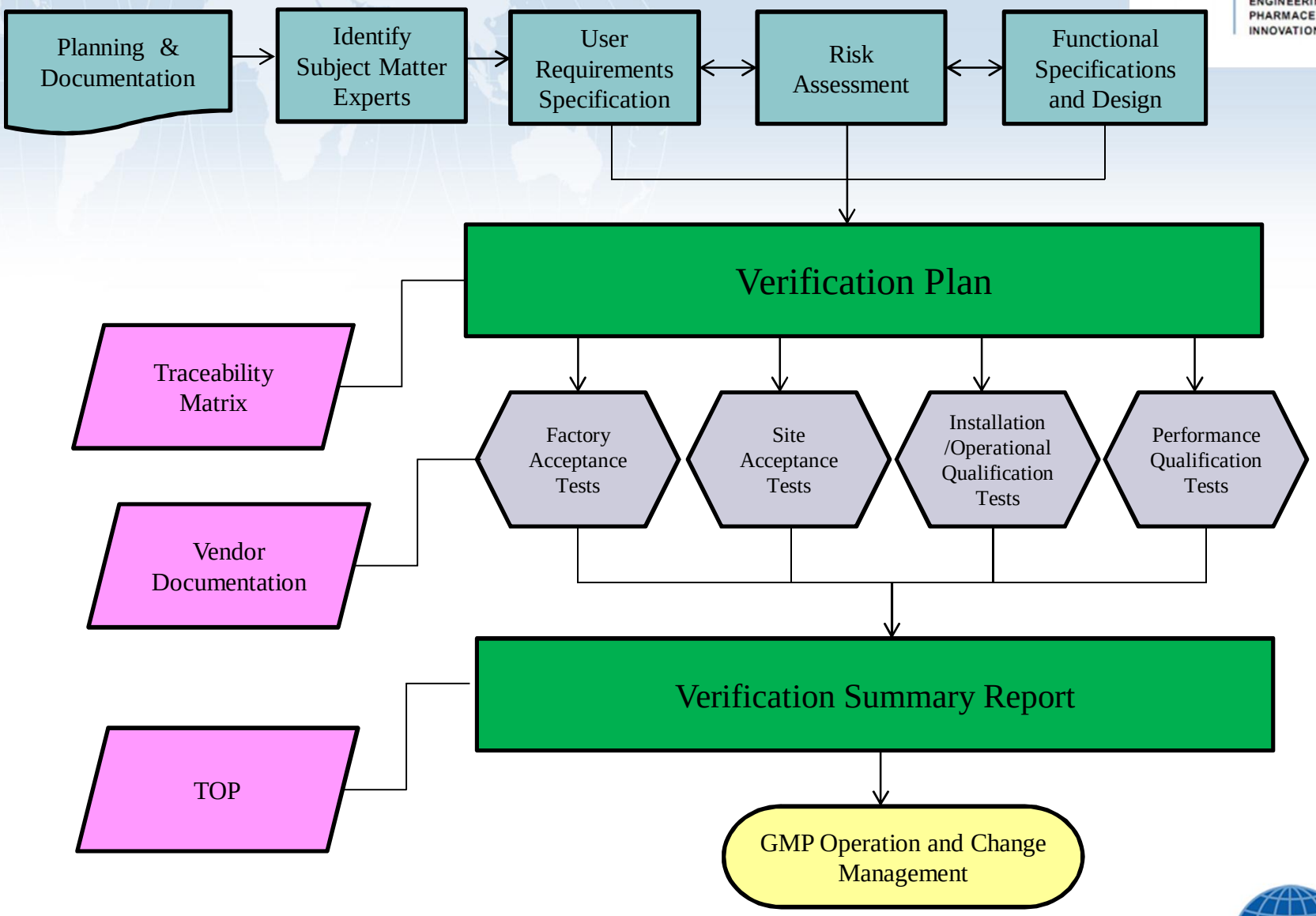

Implementation

- Planning and Documentation (VMP)
- Subject Matter Expert
- Specification / Design
- Risk Assessment
- Verification Plan
- Verification Plan Execution
- Summary Report
- Acceptance & Change Management

Subject Matter Expert

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- Individuals with **specific expertise** and responsibility in a **particular area** or field (for example, quality unit, engineering, automation, development and operations)
- In-depth knowledge of the subject, based on scientific data (QbD an Design Space), Risk assessment and scale up challenges
- With minimum 10 years of experience of design and implementation
- Knowledge of Regulatory Guidelines
- Exposure to various current topics
- Recognized by the Professionals in this field with good credentials
- Ability to coach

Specification / Design

- Based on :
  - Risk Assessment
  - Sound scientific knowledge of process and product
    - Use of QbD (CQA, CPP & CS) and Design space
  - Approved by SME
- Use vendor expertise (**SME**) to identify & **document** the critical quality attributes (**CQA**)
- Determine Acceptance Criteria

Risk Assessment

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The following can be used alone or in combination :

Risk Based

- Quality System
- Validation
- Process Monitoring
- Documentation and
- Risk MaPP

Tools

- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis And Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)

Verification Test Plan

- **Verify the critical aspects of the manufacturing system**
  - Design, Installation and Operation
  - Meets **performance** requirements and **"Fit for intended use"**
- **Identifies all required testing & documentation**
  - **Extent** of verification and documentation should be based on risk to Product **quality** and patient **safety**
  - Criticality, risk factors of URS to be verified
  - Testing occurs from ñFATò to ñPQò
- **Acceptance criteria**
  - Developed and approved by **subject matter experts**
  - **Critical aspects** approved by the **quality unit**
- ñ**Traceability Matrix**ò

  It summarizes required testing and **when** it occurs

Verification Plan Execution

- Subject matter experts perform or oversee activities, and document results
- **Leverage FAT/SAT** testing ñrather than repeating vendor activities and replicating vendor documentationò
- **Testing occurs across** FAT, SAT, IQ, OQ, PQ
- The more critical testing or additional testing may occur during IQ/OQ to mitigate risk

Verification Summary Report

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- Approved FAT, SAT, ETOP, IOQ and PQ Reports collectively provide documented verification that the manufacturing system is ñ**fit for intended use**”
- Summary Report provides an **overview of test results** and **non conformances** with **acceptance criteria**
- Completed verification documentation reviewed by qualified and independent **subject matter expert(s)**
- SME reviews overview of results and any nonconformance with **acceptance criteria**
- Systems with **critical aspects** should be approved by the **quality unit**
- SME confirms manufacturing system is **fit for intended use**
- Approved by **SME** and **Quality Assurance**

Acceptance & Change Management

- After Verification Summary Report approval, Quality Assurance issues authorization to **release the system for GMP operational use**
- As part of the system life-cycle, equipment, and procedures **are periodically reviewed.**
  - Modifications are controlled via **Change Management** throughout the system lifecycle
  - Changes are approved by **system subject matter experts**.
  - Changes to critical aspects or to aspects that affect system requirements relative to **product quality** and **patient safety** are additionally approved by **Quality Assurance**

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Questions

Thank You for Your Attention

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