

Project
Engineering
Under
ASTM E2500

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ISPE[®]

Presentation Objective

The purpose of my presentation is to look at industry expectations for GMP projects in light of the ASTM E2500 guidance. I will also look at the role of the Project Engineer in fulfilling these expectations.

Presentation Outline



- Background
- Current state of practice
- Engineering Discipline
- Review of ASTM E2500 and other relevant guides
- Project Management Process
- Practical integration of ASTM E2500 with Project Management

3

Prevailing Guidance in 2007



- ICH Q8 2005 (R1) – Pharmaceutical Development
 - Approved design space
 - Proven acceptable range
 - Control strategy
 - CPP, CQA, QTPP
- ICH Q9 2005 – Quality Risk Management
 - Evaluation of risk to quality should be based on scientific knowledge and...link to protection of patient
 - Level of effort...of the QRM process should be commensurate with level of risk.

4

Prevailing Guidance in 2007

- *Pharmaceutical cGMPs for the 21st Century – a Risk-Based Approach* (FDA), Guiding principles include:
 - Risk-based orientation
 - Science-based policies and procedures
 - Strong public health protection

- *The ISPE Baseline Guide Volume 5, Commissioning and Validation*
 - Design, construction, commissioning, and qualification of facilities
 - System Level Impact Assessments
 - Apply GEP and commissioning to Indirect and No-Impact Systems
 - Additionally apply Qualification Practices (IQ, OQ, PQ) to Direct Impact Systems

5

Prevailing Practice Today

Practitioner comments:

“The traditional validation activities have become **centered around documentation**, instead of ensuring quality...Traditional validation activities...**stifle innovation**, cause **compliance risk** and compromise a life science firm’s ability to bring products to the market on time.” 2013, Valgenesis Webpage

“The Quality Unit essentially behaved as a Quality Control unit checking, reviewing and approving almost every validation document. This created a tense and bottleneck situation.” 2012, Jose Ochoa

6

Prevailing Practice Today



Legacy guidance has not been followed as intended:

- *ISPE Baseline Guide Volume 5* provides Direct Impact Criteria but states that “These criteria should be used to inform a judgment based on the comprehensive understanding of the product, process, and nature of the system. They should not be used to replace the exercise of informed judgment by appropriately qualified personnel.” According to FSE (2011), **“The statement regarding informed judgment often has not been applied”**.

7

ASTM E2500 Intent



- **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**.
- Provide **manufacturing capability** to support defined and **controlled processes** that can **consistently produce product** meeting **defined quality requirements**.
- Subject Matter Experts (SMEs) with a technical understanding of the **critical aspects** of manufacturing systems to drive the **specification, design, and verification of facilities and equipment**.

8

Engineers are the SMEs for Facilities, Systems, and Equipment



- The industry has been slow to recognize that the SMEs with a technical understanding of facilities, systems, and equipment are **engineers**.
- In many cases, the industry does not recognize the engineering discipline.
- The term Project Engineer is rarely found in the industry vernacular – it is not even mentioned in the ISPE GPG for Project Management!

9

What is a Project Engineer?

Breaking it down:

A **PROJECT** is a **temporary** endeavor undertaken to create a **unique** product, service or result.

- PMBOK Guide

An **ENGINEER** is concerned with applying **scientific knowledge** to develop solutions for technical problems. Engineers design systems while considering the limitations imposed by practicality, regulation, safety, and cost.

- Wikipedia

10

Engineers are Wired Differently



- [Press Play here](#)

11

Project Engineering



Project Engineering bridges the boundaries between engineering and project management...**In some cases, the project engineer is the same as a project manager but in most cases these two professionals have joint responsibility for leading a project.**

- Wikipedia

12

Current Guidance shaping the GMP Project Engineer role



- ASTM E2500-07 *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems And Equipment*
- ISPE GPG: *Science and Risk-based Approach for the Delivery of Facilities, Systems, and Equipment*, (FSE Guide) 2011
- ISPE GPG: *Project Management for the Pharmaceutical Industry*, 2011
- PMI PMBOK - *Project Management Body of Knowledge*

13

Significance of ASTM E2500



- “Application of the approach...is intended to **satisfy international regulatory expectations** in ensuring that manufacturing systems and equipment are **fit for intended use**, and satisfy requirements for design, installation, operation, and performance” ASTM E2500 §5.1

14

Key concepts of ASTM E2500 - Risk-based approach



“The evaluation of risk to quality should be based on **scientific knowledge** and ultimately link to the **protection of the patient**” ASTM E2500 §6.2.2.1

15

Key concepts of ASTM E2500 - Science-based approach



Science-based approach - “**Product and process information**, as it relates to product quality and **patient safety**, should be used as the basis for making **science- and risk-based decisions** that ensure that the manufacturing systems are designed and verified to be fit for their intended use.” ASTM E2500 §6.3.1

16

Key concepts of ASTM E2500 - Science-based approach



“Examples of product and process information to consider include: CQAs, CPPs, process control strategy information, and prior production experience.” ASTM E2500 §6.3.2

17

Key concepts of ASTM E2500 - Critical system aspects



“**Critical aspects** of manufacturing systems are typically **functions, features, abilities, and performance** or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and **patient safety**.”
ASTM E2500 §6.4.1

18

Key concepts of ASTM E2500 - Quality by Design



“Quality by design concepts should be applied to ensure that critical aspects are designed into systems during the **specification and design** process.” ASTM E2500 §6.5.1

19

Key concepts of ASTM E2500 - Good Engineering Practice



“Good Engineering Practice (GEP) should underpin and support the specification, design, and verification activities.” ASTM E2500 §6.6.1

20

Key concepts of ASTM E2500 Specification, Design, Verification

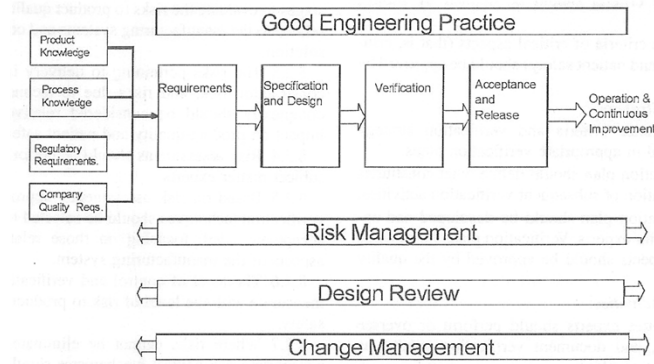


FIG. 1 The Specification, Design, and Verification Process

21

Key concepts of ASTM E2500 – Subject Matter Experts



- “Subject Matter Experts are defined as those individuals with specific expertise and responsibility in a particular area or field (for example, quality unit, **engineering, automation**, development, operations...)” ASTM E2500 §6.7.1.
- “Subject Matter Experts should take the lead role in the verification of manufacturing systems as appropriate within their area of expertise and responsibility.” ASTM E2500 §6.7.2.

22

Key concepts of ASTM E2500 - Vendor Documentation



“The decision and justification to use vendor documentation, to support the verification of critical aspects of the manufacturing element...should be documented and approved by SMEs...”

ASTM E2500 §6.8.3.

23

ASTM E2500 is only five pages
long, yet it refers to SMEs 21
times!



24



ISPE FSE Guide

The GPG Science and Risk-based Approach for the Delivery of Facilities, Systems, and Equipment (FSE Guide, 2011)

- Provides direction to industry on the implementation of a **science and risk-based approach**
- Compatible with Q8, Q9, Q10 and E2500

25



Objective of FSE

- “...to **facilitate the translation of the scientific knowledge** about the product and process into documented specification, design, and verification of equipment, systems and facilities which are fit for intended use, and minimize risk to product quality and **patient safety.**” FSE §1.2

26

FSE on SME Role



- “SMEs should take **the lead role** in the verification of manufacturing elements.” FSE §2.8.1
- “Before acceptance and release, **change management** should be applied. **This process should be managed by and changes approved by SMEs.**” §10.4

27

FSE – Typical Areas of SME



- Highlights from Table 2-1
 - Process Scientists – determine CQAs and CPPs
 - **Engineering/Technical** – specification, verification
 - **Automation SME** – develop, verify, and optimize automation and process control elements
 - Quality – develop and approve verification plans with other SMEs; compliance with site QMS
 - Manufacturing personnel – operability, SOPs

28

FSE – Tools



- FSE Appendices demonstrate tools for:
 - Risk Assessments
 - FMEA & FMECA
 - FTA
 - HACCP
 - HAZOP
 - Fishbone, etc.
 - Impact Assessments
 - Commissioning

29

FSE – Qualification Approach



FSE Appendix 14: Qualification Approaches

- Guidance on how PMs can apply [the guide's] principles...to eliminate non-value-added Qualification practices... FSE §14
- Technical SMEs can determine separately how to inspect or test a given engineering aspect, and the field work can be carried out and documented under GEP... FSE §14.2

30

ISPE Applied Risk Management Guide

The guide describes how organizations can move from established baseline practice (Volume 5) to a more efficient science- and risk-based framework (FSE).

31

PMBOK

- Describes the project management life cycle
- Recognizes 47 processes in five basic process groups and ten knowledge areas

32

Process Groups	INITIATION	PLANNING	EXECUTION	MONITORING & CONTROL	CLOSING
4. INTEGRATION	1) Develop Project Charter	2) Develop Project Management Plan	3) Direct and Manage Project Work	4) Monitor and Control Project Work 5) Perform Integrated Change Control	6) Close Project or Phase
5. SCOPE		1) Plan Scope Management 2) Collect Requirements 3) Define Scope 4) Create WBS		5) Validate Scope 6) Control Scope	
6. TIME		1) Plan Schedule Management 2) Define Activities 3) Sequence Activities 4) Estimate Activity Resources 5) Estimate Activity Durations 6) Develop Schedule		7) Control Schedule	
7. COST		1) Plan Cost Management 2) Estimate Costs 3) Determine Budget		4) Control Costs	
8. QUALITY		1) Plan Quality Management	2) Perform Quality Assurance	3) Control Quality	
9. HUMAN RESOURCE		1) Plan Human Resource Management	2) Acquire Project Team 3) Develop Project Team 4) Manage Project Team		
10. COMMUNICATIONS		1) Plan Communications Management	2) Manage Communications	3) Control Communications	
11. RISK		1) Plan Risk Management 2) Identify Risks 3) Perform Qualitative Risk Analysis 4) Perform Quantitative Risk Analysis 5) Plan Risk Responses		6) Control Risks	
12. PROCUREMENT		1) Plan Procurement Management	2) Conduct Procurements	3) Control Procurements	4) Close Procurements
13. STAKEHOLDER	1) Identify Stakeholders	2) Plan Stakeholder Management	3) Manage Stakeholder Engagement	4) Control Stakeholder Engagement	



ISPE GPG: Project Management for the Pharmaceutical Industry

“It is considered good project management practice to integrate GxP with relevant project management activities to ensure that compliance risk is managed effectively and proactively.” PMP® §1.1



Purpose of the ISPE PMPI Guide

“...to provide a reference source of good practices for project management for a wide variety of project types within the pharmaceutical industry.” PMPI §1.2

35



PMPI Alignment with ASTM E2500-SMEs

“Project Managers may need to coordinate a wide range of knowledge in pharmaceutical industry projects and may not be a SME for the project type.” PMPI §2.2.1

36



PMPI Alignment with ASTM E2500- Product Quality

Project requirements that relate to product quality are defined in ASTM E2500-07 as:

- Product knowledge
- Process knowledge
- Regulatory requirements
- Company quality requirements

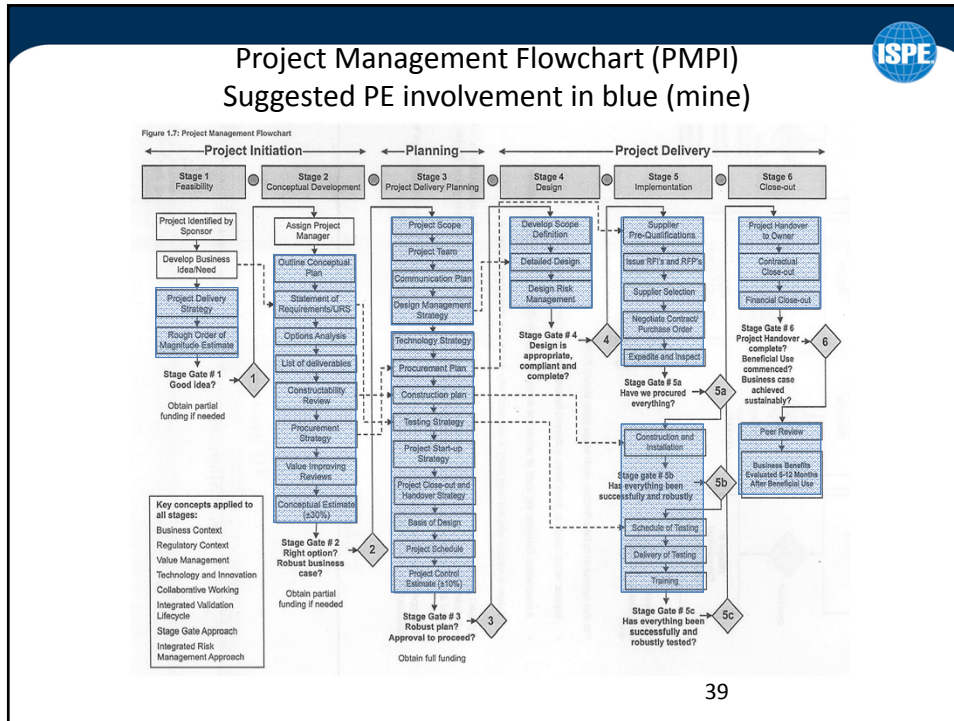
37




PMPI Alignment with ASTM E2500 A Question of Balance

“Team members need to understand their SME role and also the need to balance deliverables and expectations with cost and schedule, as the PM does.” FSE §2.4

38



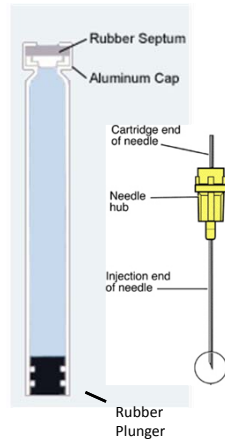
Proposed Tool – CSA Registry



The CSA Registry is a trace matrix that links CQAs, CPPs, and critical system aspects with patient safety to help meet the intent of ASTM E2500

40

CQA, CPP, Prior Production Experience, and Critical Aspects of a Manufacturing System



Cartridge and Needle



Syringe



Component Washer

41

CSA Registry - Process

- Perform an impact assessment on proposed changes, per FSE Appendix 2, to identify critical aspects
 - Collect product and process knowledge (CQAs, CPPs, etc.)
 - Determine the impact to all CQAs and CPPs for each critical system aspect
- Determine the impact to patient safety for each impacted CQA
- Develop test protocols to verify each critical system aspect and include the corresponding test references in the CSA registry
- Create a trace matrix or registry linking CQAs, CPPs, critical system aspects, and verification results to patient safety

42

Proposed Tool - Critical System Aspect Registry

Critical system	Critical system aspect	Impacted CQAs		Impacted CPPs		Verification Test Reference	Risk to patient safety
		CQAs	Acceptable range	CPPs	Acceptable range		
Component washer	Silicone dosing of plungers	Plunger force	4.5 to 6.0 newtons	Film thickness of silicone on plunger	1 - 2 microns	VT 1.1.1	High plunger force can cause cartridge to break during use
		Epinephrine concentration	5 - 7 %	Amount of silicone in solution	< 1 PPM	VT 1.1.2	Low epi concentration can cause anesthetic to wear off before procedure is complete

43

Summary


The intent of ASTM E2500 is to provide a **“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.”** The guide requires that SMEs lead this effort.

The SMEs for manufacturing systems and equipment are **engineers**.

Partnering a Project Engineer with a Project Manager can lead to more efficient and effective project delivery. It delivers on the ASTM E2500 requirement to incorporate science-based and risk-based understanding of manufacturing systems that can impact patient safety. The PM can focus on the business and administrative tasks while the PE can focus on the technical aspects.


A Critical System Aspect Registry is proposed as a new tool and process for helping to manage the life-cycle of critical systems under E2500.

44




Work Breakdown Structure

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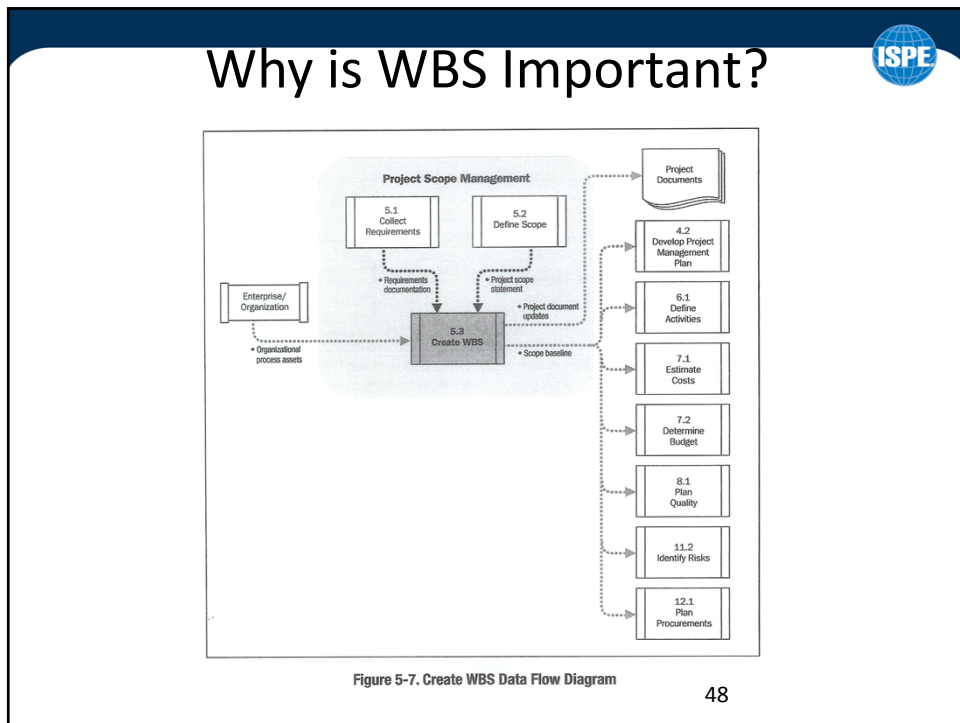
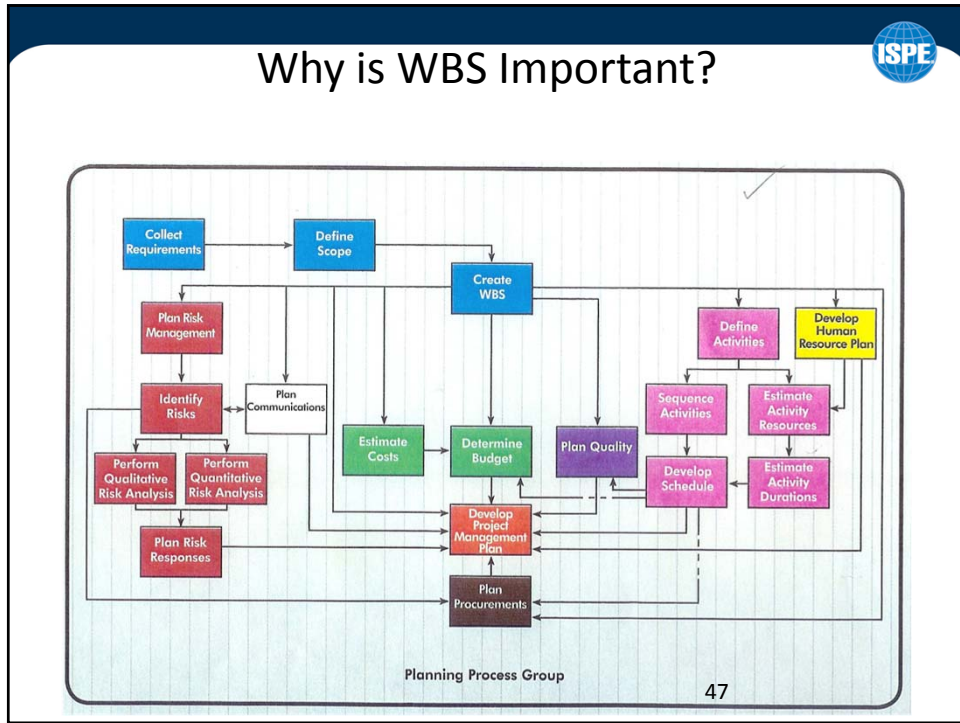


PMBOK Process Map



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46



WBS Process - Inputs



The inputs to the WBS process are:

- Project scope statement – narrative description of scope with major deliverables
- Requirements documentation – conditions and capabilities that must be met to satisfy formally imposed documents
 - The wants, needs, and expectations of sponsors, customers, and other stakeholders
- Organizational Process Assets – formal and informal policies and procedures

- PMI PMBOK Guide Fourth Edition

49

Definitions



Work Breakdown Structure - A **deliverable-oriented** hierarchical decomposition of the work to be executed

Work Breakdown Structure Component – An entry in the WBS that can be at any level

Work Breakdown Structure Dictionary – A document that describes each component in the WBS

Work Package - A deliverable or project work component at the lowest level of each branch of the WBS

- PMI PMBOK Guide Fourth Edition

50

WBS Process



Break the total project work into work packages:

- Identify and analyze the deliverables and related work required by the inputs.
- Structure and organize the WBS
- Decompose the upper WBS levels into lower level detailed components.
- Develop and assign identification codes to the WBS components
- Verify that the degree of decomposition is necessary and sufficient.

51

WBS Process - Structure



The structure can be created in a number of forms:

- First level can be project phases or major deliverables
- First level components should match, word-for-word, the **nouns** used to describe the outcomes of the project in the Scope Statement.
- Where a subproject is performed by an external vendor the vendor can supply a separate WBS for this work.

52

WBS Process - Decomposition



- Subdivide the work for each of the deliverables or subprojects into its fundamental components
- The WBS components represent verifiable products, services, or results
- Verifying correctness of decomposition requires determining that the lower-level WBS components are those that are necessary and sufficient for completion of the higher level component.
- Different deliverables can have different levels of decomposition.
- As work is decomposed to greater detail, the ability to plan, manage, and control the work is enhanced.
- Excessive decomposition can decrease efficiency.

53

WBS Process – 100% Rule



The WBS must include 100% of the work defined by the project scope. This includes all deliverables in terms of work to be completed, including project management. The rule applies at all levels within the hierarchy: the sum of the work at the child-level must equal 100% of the work represented by the parent. The WBS should not include any work that falls outside the actual scope of the project.

54

WBS Process – Code of Account

Use a hierarchical coding scheme to identify each Work Component

WBS LEVEL 1:

- 1. Bicycle_ (100)

WBS LEVEL 2:

- 1.1 Frame Set_ (15)
- 1.2 Crank Set_ (5)
- 1.3 Wheels_ (30)
- 1.4 Braking System_ (5)
- 1.5 Shifting System_ (5)
- 1.6 Integration_ (35)
- 1.7 Project Mgt_ (5)
- 100

WBS LEVEL 3:

- 1. Bicycle
- 1.1 Frame Set
 - 1.1.1 Frame_ 7
 - 1.1.2 Handlebar_ 2
 - 1.1.3 Fork_ 3
 - 1.1.4 Seat_ 3
- 1.2 Crank Set_ 5
- 1.3 Wheels
 - 1.3.1 Front Wheel_ 13
 - 1.3.2 Rear Wheel_ 17
- 1.4 Braking System_ 5
- 1.5 Shifting System_ 5
- 1.6 Integration
 - 1.6.1 Concept_ 3
 - 1.6.2 Design_ 5
 - 1.6.3 Assembly_ 10
 - 1.6.4 Testing_ 17
- 1.7 Project Mgt_ 5
- 100

55

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56