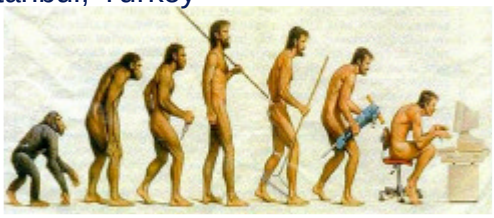
CONCEPT
HEIDELBERG

GMP Compliance for
Computerized Systems Validation
January 16 - 17, 2003 at Istanbul, Turkey

The Validation Life Cycle



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The Whats and Whys of Systems Validation

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Where Wisdom Comes From ....

" I keep six honest serving men -
They taught me all I knew -
Their names are What & Why & When
& How & Where & Who."

Rudyard Kipling

Definition II

"Providing documentary evidence that the computer hardware and software together reliably do and will continue to do what they are intended to do."

PMA CSV Committee (1986)
Validation Concepts for Computer Systems
Used in the Manufacture of Drug Products

What's incomplete in this definition?

Definition III

"Validation - the stage in the software life-cycle at the end of the development process where software is evaluated to ensure that it complies with the requirements"

Intranet Online Computer Dictionary
http://wfn-shop.princeton.edu/foldoc

What's wrong with this definition?

Definition: Validation

"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."

FDA Guidelines
on General Principles of Process
Validation (July 1987)

Computer System Validation

"Confirmation by examination and provision of objective evidence that computer systems specifications conform to user needs and intended uses, and that all requirements can be consistently fulfilled"

FDA Guidance for Industry
21 CFR Part 11, Glossary
Draft Version August 2001

What needs Validation?

New and existing computerized systems and devices which collect, process, capture, store, archive, retrieve, transmit or manipulate data that

- may be included in a submission to a regulatory authority
- are involved in manufacturing, controlling, testing, packaging, holding or distributing products or substances for human or veterinary use

Some Examples

- IT supported business application systems
- Plant control systems
- Programmable logic controllers
- Systems with embedded microprocessors
- Infrastructure elements
- Servers
- Personal computers

Configuration Elements

Application Software
- Standard Packages
- Custom developed Software
- Add-ons + Interfaces

+ A/S Documentation

Technology Products
- Hardware + Netware
- Operating Software
- Equipment + Peripherals

+ T/P Documentation

Other Documentation
- Life Cycle Documents
- Standards + Procedures (SOP)
- Logs

Personnel Matters
- People
- Organization
- Training

System Failures - Human Errors

"Computers are unreliable,
but people are even more unreliable"

" Any system which depends on
human reliability is unreliable "

Gilb's First and Second Law of Unreliability

System Failures - Human Errors

New technologies will succeed or fail
based on our ability to minimize
the incompatibilities between
the characteristics of people and
the characteristics of the things
we create and use.

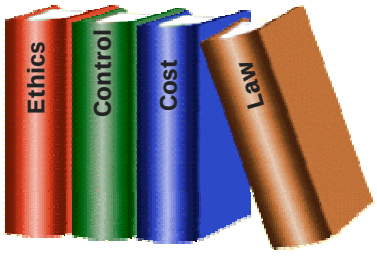
Steven M. Casey, 1993/1998
“Set Phasers on Stun”
and Other True Tales of Design, Technology, and Human Error

Hot Buttons of CSV

Essential key points that characterize a sound validation approach

- Team approach
-
-
-
-
-
-
-
-
-
-

Why Validate?



QUALITY

Ethical Approaches

- In the Pharma world:
  Maintain or restore human health and well-being
- Scientifically:
  - Assure objectivity and honesty
  - Aim to reveal and confirm natural facts and ensure their reproducibility

Jürgen Drews, 1994

➡ CSV helps to assure quality by minimizing the risk of errors and system failures

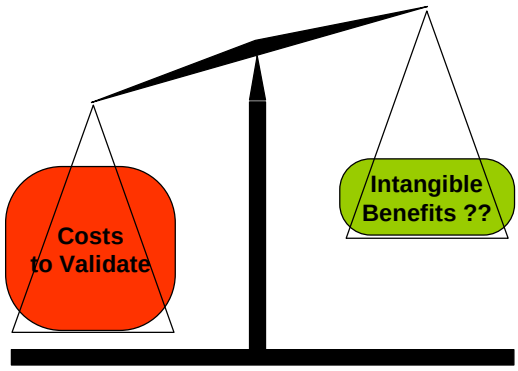
Validation for Control

- Ask your financial controller:
  What controls does our company have on our financial systems?

➡ CSV provides a framework for management control of computerized systems

➡ CSV supports to consistently get the product in right quality

Cost Considerations

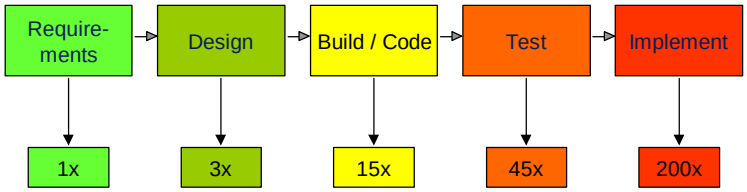


Costs to Validate

- Additional documentation
- Expenses for pure formalism
- Dependency on external expertise / consultants
- Time-consuming, expensive training
- Unlimited extra requirements

Cost Considerations

Cost factors to correct a defect:



(Barry Boehm 1981: Software Engineering Economics)

System Validation Benefits

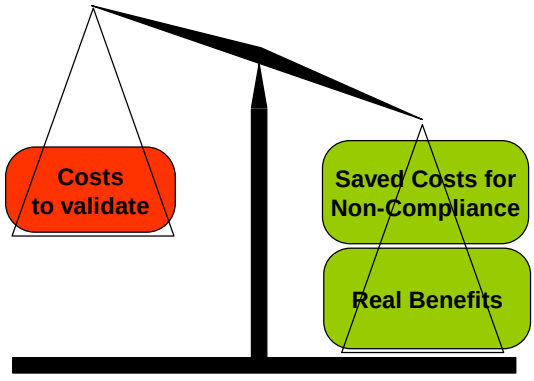
- Understanding the business
- Shortening project duration
- Reducing the risk of failure
- Involving the users from the beginning
- Harmonizing scheduling of all resources
- Lower costs for maintenance and enhancements
- Controlling the project's / application's progress
- Making our customers happy
- Improving compliance at any time
- Ensuring personal success

Realizing the Benefits

- Clarify responsibilities
- Use a structured approach (new KISS)
- Agree, establish, review all 5M* resource types
- Don't depend on outside "advisors"
- Implement risk management
- Develop in-house / external synergies
- Start validation early
- Monitor progress

* **m**an, **m**achine, **m**aterial, **m**oney, **m**inutes

Cost Considerations



Law / Regulatory Matters

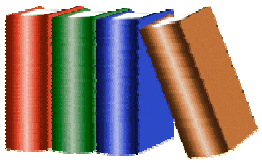
§ FDA: Guide to Inspection of Computerized Systems in Drug Processing (1983)

§ GMP for Medicinal Products in the EC, Annex 11 (1992)

§ ROCHE Project Management Guidelines, Principle 6 "All projects have to be established in accordance with ROCHE quality assurance and computer system validation policy and guidelines"

The CSV Drivers

- Ethical behavior
- Good science
- Good business
- Encouragement from regulatory bodies



QUALITY

What is a Warning Letter?

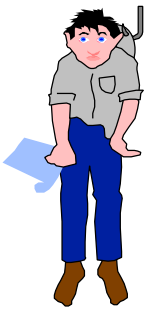
Typical Closing Statement of an FDA Warning Letter:

"If you fail to perform these corrections, FDA may execute serious regulatory action(s), which can include the permanent injunction of operations and/or individuals and the criminal prosecution of your firm and/or responsible individuals. These actions can occur with no prior warning."

Who is Responsible?

You & You & You & You

Who is Responsible?



Need a team with well-defined roles for all members, e.g. including:

- Sponsor / Owner
- \+ User
- \+ IT Professionals
- \+ Vendor
- \+ Management
- \+ QA / QC

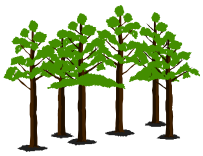
The **right** team uses the **right** people using the **right** tools at the **right** time

Companies are getting smarter or they are getting out !

How Much is Enough?

- The size and effort of a Validation task is directly related to the size and complexity of the computerized system and its application
- A high degree of confidence / assurance is all that can be attained
- Decision after risk assessment recommended

It is up to you to decide:
forest friendly or
forest unfriendly



Risk Assessment

Project Area	Risk Area	Risk Statement	Probabi-lity	Consequences	Impact	Risk Exposure	Precautions Countermeas.	Person Respons.
1	2	3	4	5	6	7	8	9
functional geograph. organiza-tional ...	**m**anpower **m**oney **m**aterial **m**achines **m**inutes		3 very likely 2 pro-bable 1 inpro-bable		4 catastroph. 3 serious 2 marginal 1 neglectible	1 ... 6		

... more on **risk** during my presentation this afternoon

Never Forget ...

"We are responsible for what we do,
but also for what we don't do"

Voltaire
1694 - 1778

Horror Stories

- The THERAC 25 radiation equipment: 4 deaths
- Siemens USA: 4 medical tech. plants to cease production for 6 months, loss > 1 billion DM
- Glaxo's NDA was not granted due to missing PLC validation
- Warner Lambert had chemical production site shut by the FDA
- Roche Nutley´s horrible Warning Letter December 1999
- ... all this cannot happen to you ??

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