A New paradigm for Single Use System (SUS) Qualification

Fully employing Process Control Risk Analysis

A Vision for the future

FASTER Qualification

- Written in a day
- Executed in a day
- No Deviations/Discrepancies

BETTER

- Clear Focus on Critical Attribute(CA) to Critical Design Element (CDE)
- Remove superfluous tests

CHEAPER

- Less Internal effort
- Shorter or reduced SOW for Contractor support

Let’s **MODERNIZE** our Qualification approach further!

History Lesson

How was the Qualification of systems done in the past?

- Custom and fixed systems
- System Impact Assessment/ Component Criticality Assessment
- Ex: Validated Chill water systems

Why ASTM E-2500 was written (2007, 2012, 2023)?

- New approach to effectively validate systems to ensure consistent product quality
- Assess effects **Patient Safety/Product Quality**
- **Science and Risk based Assessment** to determine what needed to be controlled.
  - Almost everything was custom built >> risk
  - Does the design adequately control X?
  - Main risks:
    - Controlling Critical Process Parameters-pH, DO, Flow rates
    - Contaminations –Bacterial and Particulate

Traditional Risk Assessment

Example

CA	Severity	Probalbity	detection	RPN	CDEs	IQ	OQ
pH	5	1	1	5	pH control loop	pH Instrument, Cal, alarms	pH PID tuning test
DO	5	1	1	5	DO control loop	Do Instrument, Cal, alarms	DO PID tuning test
Bacterial	5	3	3	15	SIP	traps, RTDs, alarms	SIP cycle

RPN = Risk Priority Number

In the past, Qualification of a system looked like

- Custom URS
- Specific Material Of Construction
- Custom Design
- Custom Software
- Bespoke instrumentation and control loops
- Detailed Risk Assessment with respect to every Critical Aspect

  e.g. pH, Agitation, DO, Temp, CIP/SIP systems

Novel, Risky

Recommended Approach From E-2500

"The level of effort, formality and documentation of the quality risk management process should be commensurate with the **level of risk**"

E-2500

"The extent of verification and the level of detail of documentation should be based on risk and the **complexity and novelty** of the manufacturing system"

E-2500

So why not exploited in the past?

- Custom designed
- Custom built materials
- Custom designed and built Software
- Unique instruments
- Hand build on site, or in a specialized shop.
- Everything was 1 of 1

Risk Assessment

Verify all Critical Design Elements

Companies are overly risk averse!

So.. What is different with Single Use Systems?

FROM

Custom systems

LAMBORGHINI

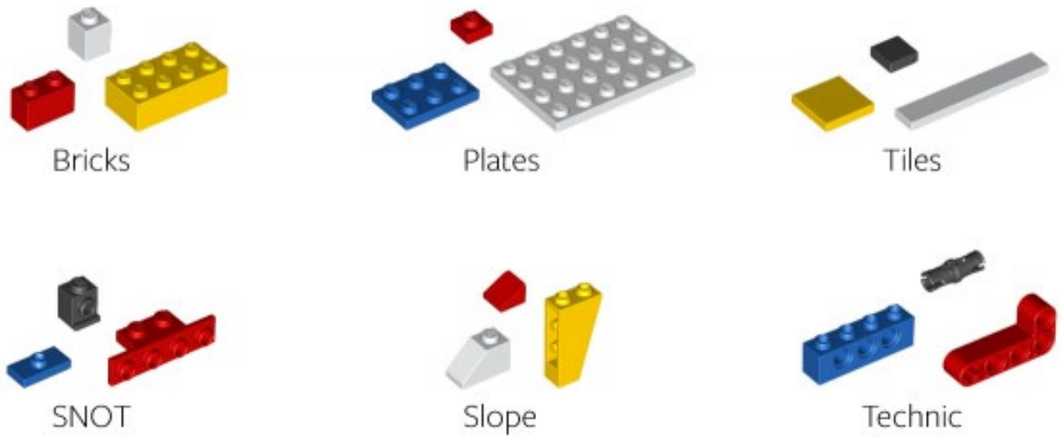
MAKE IT UNIQUE MAKE IT YOURS

Reference: Lamborghini.com, https://www.thextremexperience.com/cars/build-custom-lamborghini/

TO

Standard systems

SUS - Standardization across



Suppliers have harnessed the power of Standardization with standard…

- Software
- Instruments
- Sizes/Design
- Control loops
- Modules

Standards means:

- ✓ Decreased complexity
- ✓ Robust offering (continuously improved over many years)
- ✓ Repeated and Tested Technology

Seamless Implementation of Single-Use Bioreactor Systems

Reduce overall validation burden and time-to-facility through pre-engineered hardware and software modules.

Single controller operates all bag holder sizes, enabling modularity and space optimization. Integrated design minimizes utility requirements. Pre-configured hardware with qualified components with FAT/SAT execution and documentation

Biobrain® fully lifecycled GMP ready S88 compliant industrial software. Cross platform functionality. Qualified software interface allowing user defined configurations for different applications. CFR 21 Part 11 assessment report and connectivity guidance documents.

Industry leading Flexsafe® single-use bag technology. Ready to go validation and leachable extractables guide. Qualified bag design and robustness testing according to statistical methods. One film technology across cell culture and fluid management operations. Easy and fully qualified product configurations (CTO configured to order).

Standard Biostat STR® Configurations for PD to CM

System Type	Automation	Features & Components
Biostat STR® - Cell Culture (option for integrated Xcell ATF)	**Biobrain®** - Sartorius lifecycled software platform. (USP and DSP)	• Interchangeable bagholder sizes • Preconfigured upgradeable software • 50L – 2000L WV • PAT integrated toolbox • Flexsafe® STR bag • Integrated design
Biostat STR® Microbial	**Biobrain®** – Sartorius lifecycled software platform. (USP and DSP)	• Preconfigured flexible software • 40L WV • PAT integrated toolbox • Flexsafe® STR bag • Integrated design
Native Delta V™ STR®	**Emerson Native Delta V™** – joint Sartorius and Emerson support	• Pre-Engineered • North America preferred components • Standard Ethernet IP • Emerson standard controllers • Open source • Flexsafe® STR bag • Integrated design

We argue…

"**The Level of Risk**", as well as the "**Novelty**" of SUS are substantially lower than when we built each system, so the

- Level of effort
- Formality of Risk assessment
- Extent of Verification
- Documentation

can be reduced. Safely!!

Adding to your Risk Calculation

CA	Severity	Probalbity	detection	Novelty/complxity	RPN	CDEs	IQ	OQ
pH	5	1	1	1	5	pH control loop	pH Instrument, Cal, alarms	pH PID tuning test
DO	5	1	1	1	5	DO control loop	Do Instrument, Cal, alarms	DO PID tuning test
Bacterial	5	1	3	1	15	SIP	traps, RTDs, alarms	SIP cycle

- Adding a **Novelty/Complexity** factor will greatly facilitate the differentiation of Critical Attributes
- Quantification of “Novelty” or “ complexity” can be subjective >> data

Flow of Process

High level URS

- Process Development
- Engineering
- Regulatory
- Business
- Quality

Matched to

Vendor URS

- Vendor cut Sheet with customer cover
- Approved by Customer
- Functional User Specification (FRS)

Modified Risk Assessment

- Highlight any customization
- Minimum specification
- Additional documentations

Vendor FAT/SAT

- Pre-approved by Customer
- Test CAs/FDS
- Interoperability Testing

RTM

- Verify requirements

Process System Release

- SOPs
- Batch Record
- IOQ

Is all the risk gone?

NO!! -But we can now focus our attention where it is needed!

So, where is risk Now?

- Connections
- Set ups
- Bags & Hose assemblies

But these are Not typical IQ/OQ items >> Need to get to Verification and PQ runs.

How to get to the important Stuff…

	IQ	OQ	Eng runs	PQ	PV
Chronologically	1	2	3	4	5
Inspectors/Reality	5	4	3	2	1

- Shift Away from IOQ of system
- Focus on Integrated Testing
  - Operations/SOPs/Trng
  - Hose assemblies
  - Water runs
  - Media runs

Major Savings using our proposed approach

Cost comparison per approach

Traditional

- URS- 40 HRs
- IOV-40 hrs write
- IOV-60 hrs execute
- IOQ- 40 hrs write
- IOQ- 60 hrs execute.

- 200 hrs- @$125/hr = **$25,000**

Proposed Structure

- URS- 10 Hrs
- IOV- 5 hrs (leverate SAT)
- IOV -60 hrs Execute WITH Vendor
- IOQ- 10 hrs write
- IOQ- 5 hrs execute

90 hrs @125/hr = **$11,250**

Thanks!

Contacts:

Louis J. Traglia
Principal Consultant
28 Sep Consulting

louis.traglia@28sepconsulting.com
860-334-2106

Marion Glenn
Director CMC, Resilience

Marion.glenn@resilience.com

Resources:

E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment (astm.org)