SANITARY DESIGN: Are we straying from best practices?

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ISPE Product Show
Track 1, Session 2
September 26, 2018

BEST PRACTICES FROM 40 YEARS AGO

Excerpts from an ISPE Water System Design Presentation made in 1978

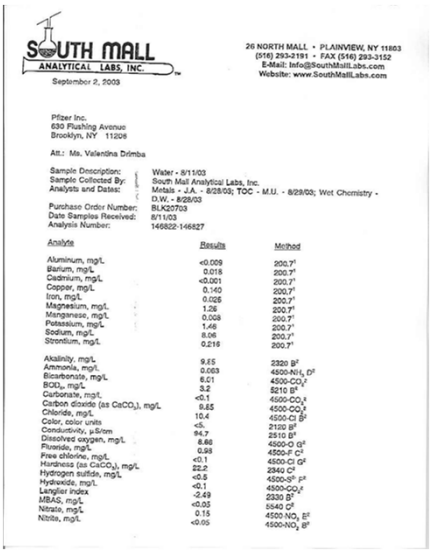
1) Determine user water requirements including quality and capacity
2) Analyze the feedwater to determine the treatment unit-operations required
3) Design the system including suitable storage and distribution to meet:
   a) Total and instantaneous demand
   b) Velocity requirements
   c) Pitch & drainability
   d) Sanitary standards for equipment and components in product contact including materials and finishes
   e) Sanitization methodologies planned (common for more than one option)
4) Installation
   a) Materials procurement, handling, erection, testing, cleaning, passivation
   b) System start-up, commissioning, and training
5) Validation

Changes over multiple decades

- **User Requirements**
  - Little or no specification change (excluding Highly Purified Water and recent EU change to WFI production)
  - Greater clarification provided by regulatory (USP)
  - Formal URS Documents with limited standardization (documents range in size from 4 to 300+ pages)
  - Vendors now offer a limited number of “standardized” equipment packages (rather than each job being customized). Extra cost for witnessed FAT, etc.
  - Limited (but greater) implementation of “Risk Based Approach” from FDA initiative.

Changes over multiple decades

- **Feed Water Analysis**
  - Feed water testing is nearly unchanged
  - Design often based on only one analysis (still!)
  - Robust designs mitigate most seasonal variations
    - Greater cost
  - Issues arise when dramatic restrictions implemented
    - California & South Western US
    - Puerto Rico
  - Standardized designs can result in higher costs
    - Designs should be more reliable
    - Greater reliance upon on-line instruments



SOUTH MALL ANALYTICAL LABS, INC.

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September 2, 2003

Pfizer Inc.
630 Flushing Avenue
Brooklyn, NY 11206

Att.: Ms. Valentina Drimba

Sample Description: Water - 8/11/03
Sample Collected By: South Mall Analytical Labs, Inc.
Analysis and Dates: Metals - J.A. - 8/28/03; TOC - M.U. - 8/29/03; Wet Chemistry - D.W. - 8/28/03
Purchase Order Number: BLK20703
Date Samples Received: 8/11/03
Analysis Number: 146822-146827

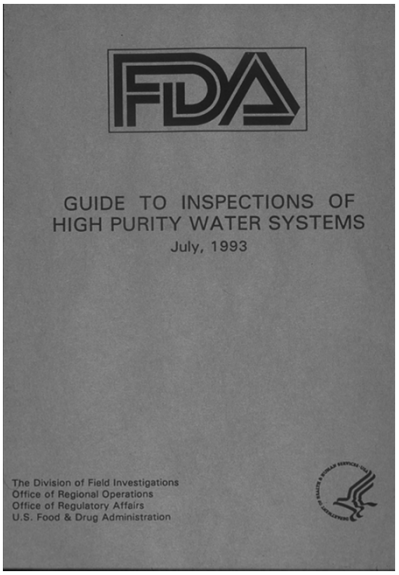
Analyte	Results	Method
Aluminum, mg/L	<0.009	200.7[1]
Barium, mg/L	0.018	200.7[1]
Cadmium, mg/L	<0.001	200.7[1]
Copper, mg/L	0.140	200.7[1]
Iron, mg/L	0.025	200.7[1]
Magnesium, mg/L	1.26	200.7[1]
Manganese, mg/L	0.008	200.7[1]
Potassium, mg/L	1.46	200.7[1]
Sodium, mg/L	8.06	200.7[1]
Strontium, mg/L	0.218	200.7[1]
Alkalinity, mg/L	9.55	2320 B[2]
Ammonia, mg/L	0.063	4500-NH_3 D[2]
Bicarbonate, mg/L	6.01	4500-CO_2[2]
BOD_5, mg/L	3.2	5210 B[2]
Carbonate, mg/L	<0.1	4500-CO_2[2]
Carbon dioxide (as $CaCO_3$), mg/L	9.65	4500-CO_2[2]
Chloride, mg/L	10.4	4500-Cl B[2]
Color, color units	<5	2120 B[2]
Conductivity, µS/cm	94.7	2510 B[2]
Dissolved oxygen, mg/L	8.68	4500-O G[2]
Fluoride, mg/L	0.98	4500-F C[2]
Free chlorine, mg/L	<0.1	4500-Cl G[2]
Hardness (as $CaCO_3$), mg/L	22.2	2340 C[2]
Hydrogen sulfide, mg/L	<0.5	4500-S^{2-} F[2]
Hydrazide, mg/L	<0.1	4500-CO_2[2]
Langlier index	-2.49	2330 B[2]
MBAS, mg/L	<0.05	5540 C[2]
Nitrate, mg/L	0.15	4500-NO_3 E[2]
Nitrite, mg/L	<0.05	4500-NO_2 B[2]

Changes over multiple decades

- **System Design**
  - Little change to demand calculations
  - Velocity requirements vary significantly (less rigid)
  - No change to pitch and drainability requirements
    - Over emphasis on pitch
  - Sanitary/Hygienic standards, materials and finishes
    - Significantly less stringent testing & verification
    - Inconsistent component specifications
    - Less importance associated with finish
  - Less frequent design based on multiple specified modes of sanitization
  - Fewer design errors based on greater familiarity

Changes over multiple decades

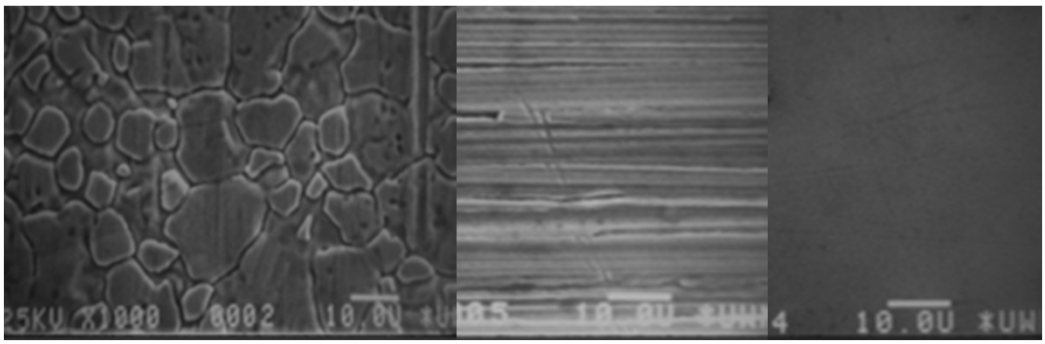
- **System Design – Impact of Changes**
  - Velocities vary from >5 FPS to <0.2 FPS depending on selected criteria (25X variance)
    - Unclear as to impact and understanding
  - Greater importance inappropriately assigned to slope than to other important design features (ie: dead-legs, materials, welding, velocity)
  - Dramatically less testing and verification of product contact surface finishes and quality. Wide disparity in specified finishes (ie: #4 / 35Ra to 5µ inch with EP)
  - Cost/budget limitations appear to have driven quality specifications to lower levels – possible risk increase
  - Sanitization frequency reduced – risk?



Surface Finish

Water systems usually do not fail because the surface finish of the equipment isn't polished to a specific quality

- Finishes ranging from 35 µ inch Ra (dairy) to 3-5 µ inch Ra EP may be acceptable in pharma water applications

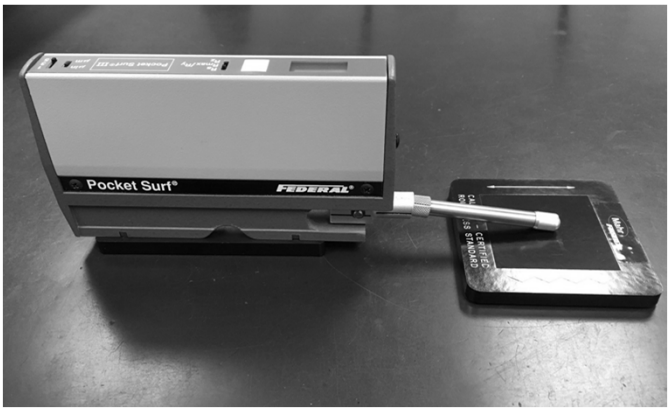


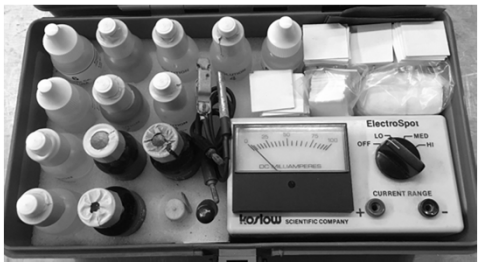
#1 - Surface Finish Measurement/Verification – Profilometer

#2 - Passivity Test Kit

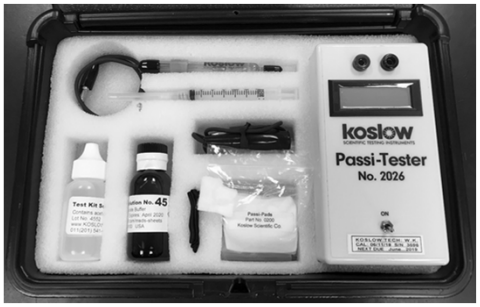
#3 - Metal Verification

#1





#3



#2

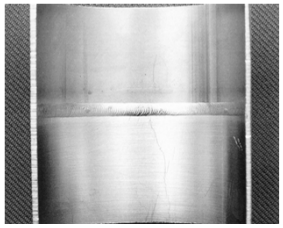
Changes over multiple decades

- **Installation - Impact of Changes**
  - Less owner and third-party inspection with greater self inspection by installers. Lower levels of inspection (ie: percentage of welds) required, often formula based.
    - Less stringent review of MTR's, Weld documentation (including videos)
    - Less stringent welder and equipment qualification
    - Less likely errors will be discovered and corrected if found.
    - Less control of materials including sourcing, receiving, inspection, rejection, etc.

Inspection formula (Example #1 Specification)

Welds in hygienic lines require 100% internal visual examination, all welds that can not be inspected by a mirror, must be inspected by a borescope. All welds require external visual examination. Tubing 1/4 inch (15 mm) diameter or less is generally not accessible for internal examination and will require blind weld coupons

Video recording of every weld is required for third party inspection.



Inspection formula (Example #1 Specification)

The piping contactor will carry out all necessary non-destructive tests, to ensure that the welds satisfy to the requirements of the sanitary piping for clean pharmaceutical services.

For Water For Injection (WFI) and Aqua Purificata Water (APW), the minimum level of tests/ examinations will be as follows:

Automatic welds:	0% radiography (X-ray)
	50% internally inspected with boroscope
	100% externally visually inspected
Manual welds:	spot X-ray (10%)
	100% internally inspected with boroscope
	100% externally visually inspected

When one weld in a pipe is not satisfactory, then 20% must be tested, including 5 welds before and 5 welds after the one defect weld (if made the same day). When these also show a too high rejection rate, then the complete pipe must be removed and a new pipe welded.

Inspection formula (Example #2 Specification)

3.4.2.5 Inspection and Testing

All fabricated tubing shall, as minimum, meet the examination, inspection and testing requirements of the applicable ANSI/ASME B31 code or the comparable EU code. The visual welding inspection shall be performed as follows:

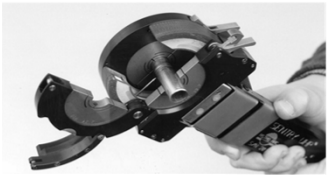
- 100% ID & OD inspection of all dummies welds.
- 100% OD inspection of all welds, and verification that each weld has been marked with its weld number adjacent to the actual weld.
- 100% borescopic inspection of the first 55 consecutive welds is a minimum per welder per machine. If no rejections are encountered, the frequency of borescopic inspections may be reduced to 25% of the welds, which shall be sampled as follows:
  - Divide the series of welds into sets of 8 consecutive welds.
  - Select two non-consecutive welds from every set of 8.
  - Verify that there is no case where the last weld of one set and the first weld of the following set are both sampled.

Inspection formula (Example #2 Specification)

- If a defect is found when inspecting at the reduced rate, the welder must return to 100% inspection for the next (55) consecutive acceptable accessible welds before again being eligible for working under the 25% rate of borescopic inspection.
- When a failure is encountered the previous weld is to be borescoped. This will continue until an acceptable weld is found.
- All welds which are identified prior to welding, as being difficult shall be borescoped. A failure of this weld does not require re-qualification of 55 consecutive welds.
- In general, weld repair is discouraged. If the weld has correctable flaws a second weld pass may be made to correct the flaw. (The weld needs to reach ambient temperature before the second pass). If the re-welding does not remove the flaw, the weld shall be rejected and cut out.
- All manual welds shall be inspected (ID and OD).

Welder Qualification

Welders will also be currently certified on the established weld schedules (as established in Section 3.6) for the job based upon submittal of at least 3 sample welds (from automatic tube welder, 2G or 5G positions shall be represented) made on different sizes of stainless steel tubing. If hand welding is accepted, 1 hand weld samples will also be required. Each weld shall meet Owner's (or Owner's representative) evaluation of weld quality. Hand welds require written approval from Owner or Owner's Representative. Contractor must submit a procedure to be approved by Owner prior to acceptance of any Hand Welds.



Validation Changes over multiple decades

- **Validation is no longer a checkbox activity. Warning Letters and Consent's Degrees issued by FDA has changed the content of validation deliverables. FDA actions along with GAMP5, ASTM E-2500 Standard and the increased interested of regulators in data integrity protection have had a profound impact. Regulators expect a set of validation deliverables including a PVP or Val Plan.**
- **Parke-Davis Consent Degree of 1993; Wyeth-Ayerst Consent Decree of 1999; and Schering Plough Consent Decree of 2002; changed the content of protocols. Detailed qualification template considered by FDA to be best practice.**
- **The issuance of 21 CFR Part 11 in the 90's and the recent issuance of draft Data Integrity Guidance from FDA and EMEA has created a data security focus. Data stored on PLCs and SCADA used to make GXP decisions, is expected to be secure and have appropriate tested security controls. A Part 11 complaint audit trail is always expected for these systems.**
- **ASTM E2500 set a precedence for leveraging commission documentation, (FAT, SAT, and Start-up Reports). More formal Project Validation Plans are being issued detailing activities, including commissioning, that provide a blueprint for activation of new systems.**

Validation Changes over multiple decades

- **Early by-in by QA is sought, so that testing is not repeated. OQ Test Case should have numbered steps, and procedure (to allow non-author to execute), expected results and space to record actual results.**
- **Risk Assessment to identify what tests should be included (what is necessary vs. not really needed). Increasingly vendors are offering testing documentation to meet the new requirements.**
- **The role of professional organizations, updating best practices and testing standards, has assisted in improving the testing and qualification process.**
- **Decreased engagement by the system owner (ex: hire a 3rd party service to represent them at FAT, SAT and/or IOQ). Lack of engagement by the primary user often leads to slow SOP, Work Instruction, and PM program development with delays in bringing the system under change control.**
- **Owners/approvers are not reading the documentation they are signing. This can become more problematic if poor (and often) low cost 3rd party documentation contactors are employed.**

Water System Axioms

Statement	True	False
USP Water must be made from water complying with US-EPA-NPDWR	X	
Tanks must be equipped with spray-balls		X
Every pipe in a water system must be sloped 1/8” per foot & be fully drainable		X
Only 316LSS is acceptable in contact with USP Grades of Water		X
FDA does not allow filters to be installed in recirculated loops or at points of use		X
Thermophiles can grow in pharmaceutical water systems		X
Periodic sanitization is needed even if the system is kept continuously under sanitizing conditions		X
No added substances are allowed. Ozone is an added substance	X	X
Dead-legs must be less than 6D		X
Water velocity must be at or above 5, 3, 1 FPS, must be recirculated and exhibit turbulent flow conditions.		X
Only diaphragm valves are acceptable – No plug, gate, ball, disk, butterfly, or globe valves		X
Reverse Osmosis and Ultrafiltration are not suitable to produce WFI		X

Water System Axioms

Statement	True	False
Vents must be equipped with sterilizing filters (.2µ & integrity tested)	X	X
PW is the required feedwater for WFI		X
Only use-point fittings or GMP style valves are acceptable for user delivery		X
Only sanitary pumps with casing drain, 45 degree vertical discharge & non-carbon seals are acceptable. Double flushed seals required for WFI.		X
No component in the system may worsen the bacteria load		X
Only sanitary clamp joints or orbital welds are allowed in water contact. Clamp joints should be minimized.		X
All drains must be air-gap type	X	
Product water must be maintained in sanitary/hygienic components		X
Sanitary finish is required to maintain water quality. Sanitary finish reduces biofilm adhesion.		X
Biofilm grows in any environment		X
Continuously hot systems experience the lowest micro burden	X	
Welded tube is inferior to seamless tubing for water systems		X

Water System Axioms

Statement	True	False
Diaphragm valves should be used in Pure Steam applications		X
Off-line conductivity & TOC testing is required even with on-line installed instrumentation		X
Low ferrite stainless steel is a necessary to eliminate rouge		X
Rouge does not impact water quality or equipment		X
Passivation is required only once when the system is put into service		X
Derouging is not required for effective passivation		X
Pure steam systems do not need to be sanitary	?	
Micro sampling of Pure Steam and WFI vapor is necessary		X
System performance and trending is irrelevant, only results below action levels are important		X
If you drink WFI you will die		X

COMMON MISCONCEPTIONS!

Delivery rate is <u>not</u> equal to flow rate through the distribution system (Maximum instantaneous demand ≠ loop recirculation rate.

Continuous flow is desirable and usually required at some minimum level:

Example:

a) Minimum Velocity 3-5 FPS
   a) 5 FPS in 3" OD tube is 101 GPM Min. (no use) approx.
   b) 3 FPS in 3" OD tube is 61 GPM Min. (no use) approx.

b) Reynolds Number indicating turbulent flow
   a) Reynolds Number of 2400 (Min. for turbulent flow) produces a velocity of .108 FPS or 2.2 GPM approx.
   b) Reynolds Number of 3000 (Alt. Min. for turbulent flow) produces a velocity of .135 FPS or 2.7 GPM approx.

COMMON DESIGN & OPERATIONAL MISTAKES

- **Failure to consider time (duration) system will operate at minimum flow**
- **Pressure drop at system flow not at maximum demand**
  - Special charts for sanitary materials
- **Estimated time needed to make changes/modifications**
  - QA/QC, Validation, Testing
- **Activities & events that will result in system downtime.**
- **Equipment obsolescence and parts availability**

Thank you!

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