# Succeeding a Regulatory Inspection on water systems

*PDA Israel*

*New Developments in Water Systems*

*Tel Aviv, May 2019*

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## Agenda

1. Indroduction
2. Pre-Inspection
3. Tour of the facility
4. Sampling
5. Maintenance
6. Routine system reviews
7. Examples of Warning Letters

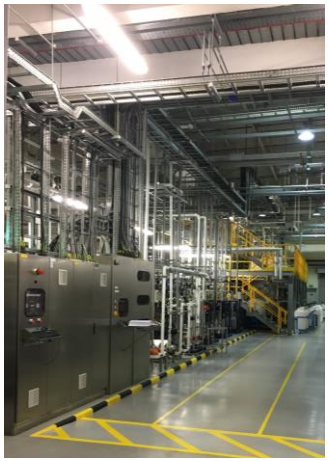
- Being constantly audit ready, reduces the disruption that an audit has on an organization and also **places the organization in control** over how the audit is conducted.
- It also means that before any audit takes place, the organization are **fully aware of their risks and has the right controls in place**.

- The life cycle of a sufficient GMP operating system starts from the **design** phase of the system and concludes in the **daily maintenance activities.**
- Recognize that **Maintenance** and **QUALITY** are also your main consumers.
- Finding the balance between quality and operational requirements to ensure vigorous system operational and quality performance.


Used with permission from Don Mayne. Wretched Mess Research Cartoons(2009)

**Overall housekeeping of the facility**.

- An untidy facility implies a disregard for good manufacturing practices and alerts the auditor to look for other poor manufacturing processes that could directly affect product quality.
- It must be remembered that anything out of the ordinary, will stimulate questions from the auditor.

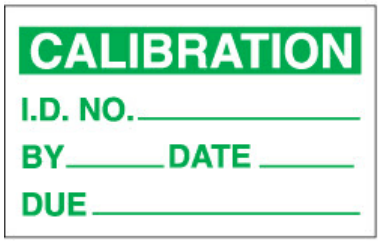


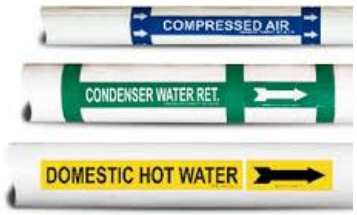

**SOPs and Logbooks**.

- Review of logbooks insuring data integrity:
  - A logbook exists for each system, and is not empty!!
  - No empty fields, no missing dates or signatures.
  - All activities are documented and reveal the true state of the system.
- Procedures may be centrally located or even hanging or posted in the area where they are used. These must be the currently effective procedure versions.
- Documents should be inspection ready state at all times, with minimal effort required to prepare for an inspection.

**Equipment and Piping Condition and Tagging**.

- Equipment, gauges/sensors, valves, sampling valves, piping must all be clearly and unambiguously tagged or labeled.
- There must not be multiple tags for the same gauges, ports, or equipment
- Calibration stickers must be clearly visible on critical gauges or sensors subject to calibration.
- Insulation on piping that is worn, stained, or disintegrating, the piping stained or crusted with corrosion, or the valves dripping or in an apparent state of disrepair.

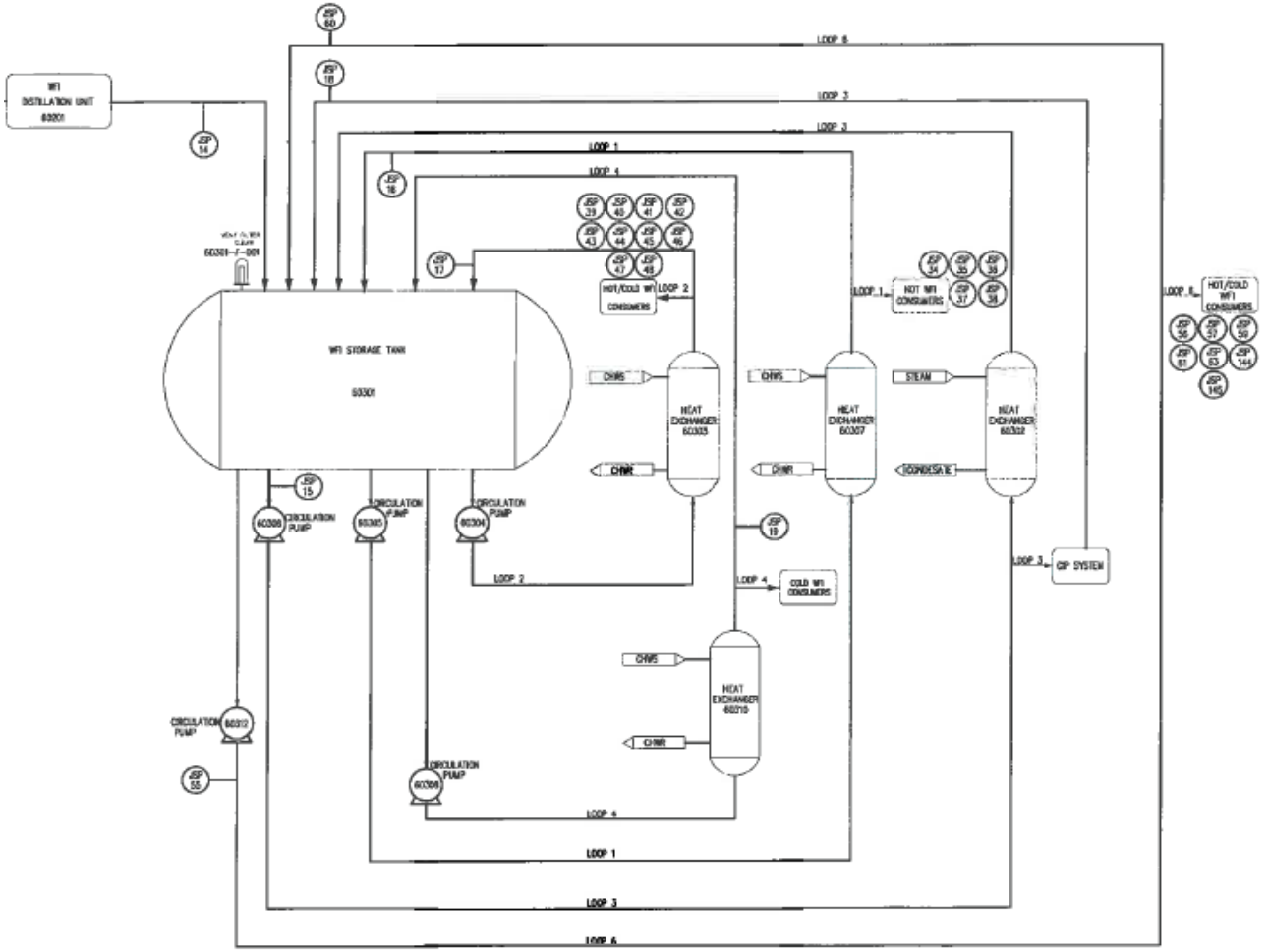



## DRAWINGS

- Review Drawings to assure they are an accurate reflection of what is installed in the field, and updated to reflect system modifications and changes.
- A Process Flow Diagram provides an overview of the system in a simple perspective, which includes system points of use and sampling points. (including On line measurements for TOC and conductivity).

## DRAWINGS


WFI DISTILLATION UNIT 60001
WFI STORAGE TANK 60301
HOT/COLD WFI CONSUMERS
HOT WFI CONSUMERS
COLD WFI CONSUMERS
CIP SYSTEM
HEAT EXCHANGER 60305
HEAT EXCHANGER 60307
HEAT EXCHANGER 60302
HEAT EXCHANGER 60310
CIRCULATION PUMP 60306
CIRCULATION PUMP 60305
CIRCULATION PUMP 60304
CIRCULATION PUMP 60312
CIRCULATION PUMP 60308
CHWS
CHWR
STEAM
CONDENSATE
LOOP 1
LOOP 2
LOOP 3
LOOP 4
LOOP 5
LOOP 6

**SAMPLING PROCEDURE:**

Capturing in procedures precise and complete details, including:

- Dedicated vessels for each type of test.
- Pre-flushing specifications (flush duration or volume).
- Frequency
- Action and Alert Levels
- Samples taken daily on a rotary basis
- Activities required following Alert/Action Levels obtained

Vague procedures invite variable execution and variable test results.


## INVESTIGATIONS AND CAPAS

- A complete list of all investigations for the system over a period of time (typically 2 years or since the end of the last inspection).
- Personnel should refresh themselves on the complicated investigations prior to the inspection.
- Should also include the CAPAs and effectiveness checks.
- Ensure that all CAPAs and checks are closed within the required due date or that any required extensions of those dates have been properly documented and assessed for any additional risk.
- Where possible, investigations and resulting CAPAs and effectiveness checks should be closed prior to the inspection.

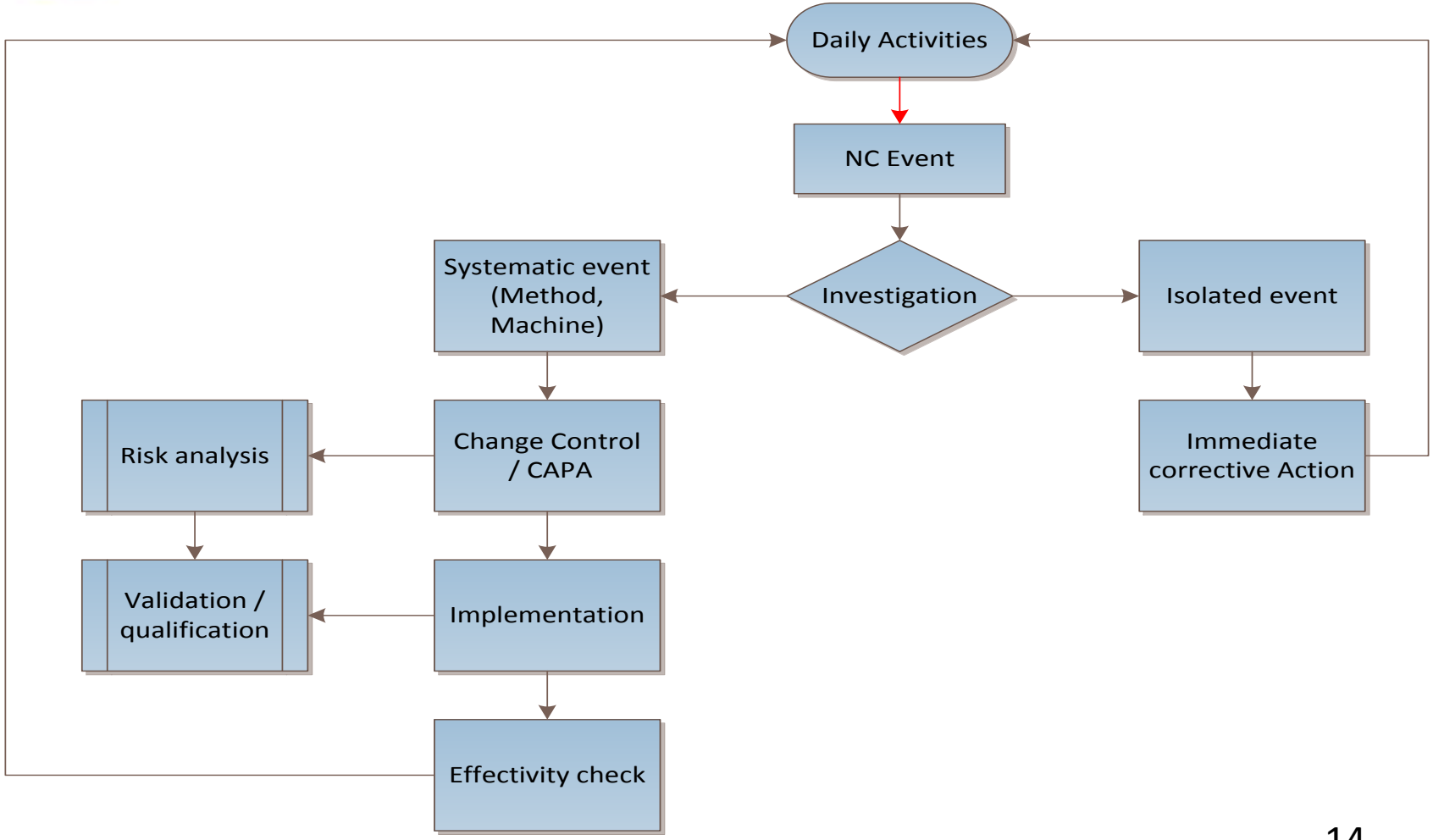
## CHANGE CONTROL

- A complete list of all Change Controls for the system over a period of time (typically 2 years or since the end of the last inspection).
- Personnel should refresh themselves on the Change Controls prior to the inspection.
- Ensure that all changes are closed within the required due date or that any required extensions of those dates have been properly documented.
- Where possible, Changes and effectiveness checks should be closed prior to the inspection.

## VALIDATION

- Validations should demonstrate the assessment of risk to establish the validation scope and sampling plans, qualification of the equipment and documented verification of system performance.
- Variables and sampling plans to consider during the validation are derived from the risk analysis, and document in the validation protocol and report.

# PRE-INSPECTION



## ROUTINE SYSTEM REVIEWS - **Annual Review**


Intended to assess the overall quality of the Critical utility Systems

- Overview most recent annual review.
- Follow up on previous annual review recommendations and their implementation
- Take account of Maintenance Activities and reoccurrence of events

## TOUR OF THE FACILITY

- The “tour guide” should be an **experienced senior Engineer** knowledgeable of the Critical utility systems as well as other utility systems.
- **Quick, authoritative verbal response** of potentially inaccurate information versus a tentative response deferred to an SOP for verification.
- A response of “as needed” with an undetermined frequency will surely instigate the auditor’s trip to log books to determine actual use periods and a request for SOPs for future reference to be used in reviewing investigations.

## POTABLE (FEED) WATER

Potable Water must comply with appropriate regulatory requirements (such as WHO, etc.) and is the minimum quality of water to be used in Pharmaceutical Manufacturing according to the USP and cGMPs.

Basically, if the water is not fit or safe to drink, it is not fit or safe to use in Pharmaceutical Manufacturing.

It is the user's responsibility to have, by some means assurance of ongoing compliance.

## PRETREATMENT

- Sampling locations should be included before and after each unit operation for diagnostic purposes so that monitoring can be performed as required.
- Sampling before and after individual unit operations helps in establishing a unit operation's performance.
- There is no regulatory requirement for limit levels or frequency, but a rationale should be developed for the sampling frequency and limit levels during the PQ and concluded in a report for routine sampling plan.

- **Examples of good water sampling and water use practices that can mitigate the microbial contamination often causing excursions:**

  - Vigorously pre-flushing water through the use port (9ft/sec ~ 2.5 m/sec).
  - Properly disconnecting and storing a reused sampling hose. (better always using a fresh sterile hose for any water transfer)
  - Sanitizing that use port valve, whenever the water system is sanitized by flushing the sanitizing agent through.
  - Implement tours with the samplers during sampling performance.

- **Features that frequently contribute to contaminated samples:**
  - The sampling hose is poorly oriented during storage so that water can puddle within or not drain efficiently.
  - Allowing the end of the sampling hose to contact the floor.
  - Using very long sampling hoses.
  - Having long unrefreshed use periods.
  - Sample point close to floor, pathway or door.
  - Poorly sequenced valve actuation in connecting piping from water systems that traps water within the piping

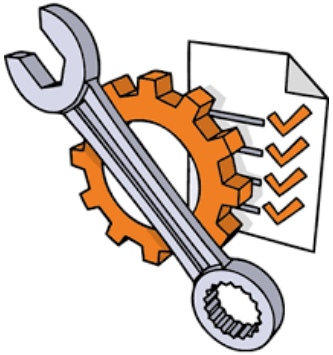
# SAMPLING

## SAMPLING PLAN

- Outlets that are used, perhaps infrequently or for perceived inconsequential purposes, but are not sampled.
- The lack of sampling could be due to inconvenience and possibly compounded by a design deficiency:
  - No installed sampling port near the equipment end.
  - No possibility for pre-flushing.
  - Can't be easily sampled due to high flow rate
  - No convenient way to reach the sample point.
  - A perceived risky area for outlet flushing
- WFI outlet being used and not sampled requires a thorough risk analysis to "forgive" this otherwise unacceptable scenario.

## MAINTENANCE

- **Maintenance Program -** Documentation to demonstrate the scheduling and completion of maintenance programs, including detailed task descriptions and evidence of personnel training.
- **Calibration Program -** documentation to demonstrate the scheduling and completion of the calibration program. Including tolerances (that cover the operating range of the instrument.), calibration frequencies and test methods.



- **Management of Planned System Shutdowns and Startups -** documented approach to tracking the completion of all critical maintenance work and calibrations against scheduled maintenance plans during planned shutdowns. Start-up plans post shutdowns that include monitoring and review of process data and QC sampling results.
- **Emergency System Shutdown/Startup Procedures**: The response taken during emergency shutdowns/startups of critical utilities should be documented and the impact on product quality should be assessed and approved before equipment is returned to operation. This documentation may take the form of a procedurally required risk assessment or be included as part of a deviation investigation.

## ROUTINE SYSTEM REVIEWS

**Daily Logs -** Depending on the level of automation used as a site, daily logs could be manual (paper based) or automated systems.

**Alarm Logs -** All automated systems will have the ability to monitor critical process parameters or critical quality attributes and should have established alarms conditions to notify users of any discrepancies or OOS events.

**System Trending** - The trending of critical process parameters or critical quality attributes should be established for utility systems

**TOUR WITH YOUR USERS !**

**A. API Manufacturing Facility 2018 – FDA Inspection**

**1. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure your API complies with established specifications and standards.**

Our investigator found that your firm was falsifying laboratory data.

For example, the number of colony-forming units (CFU) found on plates for water point-of-use tests differed substantially from the number recorded on your water report.

For multiple points of use, your analyst reported far fewer CFU than observed on the plate by our investigator.

In addition, while you reported absence of growth on a selective media plate used to detect objectionable microorganisms, our investigator observed growth on this plate.

**API Manufacturing Facility 2018 – FDA Inspection**

**2. Failure to properly maintain equipment and to keep complete records of major equipment maintenance.**

Our investigator found damaged product-contact surfaces on your multi-product equipment. For example, the manhole gasket was deteriorating and wrapped in peeling tape. A gasket was also cracked in one area and wrapped in peeling tape.

Your SOP *Gasket Management for Equipment and Pipelines which are in Direct Contact with the Product*, requires you to replace gaskets in critical areas. Your firm was unable to provide gasket replacement records for this equipment during the inspection.

violated own written procedures

Furthermore, the most recent records of your firm checking the condition of the gaskets were from January 2017. This is a repeat observation from our February 2015 inspection. We also note that you have found deteriorating gaskets to be the root cause for finished API particle complaints.

**B. Cosmetic firm failed to investigate test results showing industry 2018 – FDA Inspection**

Your that your water exceeds the allowable limit for microorganisms.

Your tests on samples from your water system indicated that microorganism levels were too numerous to count (TNTC) on 25 out of 96 days. You use this water as a major component in manufacturing over-the-counter (OTC)

drug products. Your failure to investigate violated your written procedures which require an investigation when results are above 'x' cfu/mL.

Your response is inadequate because quality control testing of a limited sample is insufficient to establish that a product is acceptable. Because microbiological contamination is not uniformly distributed and difficult to detect during testing.

Your response is also inadequate because it did not address your failure to investigate the frequent, excessive levels of microorganisms in your water system. You did not explain how you will ensure adequate and effective investigation of out-of-limit test results moving forward.

**C. Global Pharmaceutical Company - 2017 – FDA Inspection**

*Failure to Validate Purified Water System*

You have not validated the purified water system that you have been using for at least three years to manufacture products that are ingested, inhaled, or applied topically. Some of these products are indicated to treat irritated tissues or wounds that may be more vulnerable to infection. Although you partially documented the results of validation activities you conducted in 2013 following relocation of your water system in a report dated April 28, 2014, your report does not include the results of microbiological tests that you performed during your validation activities. The same report states the microbial load of your purified water system steadily increased following the validation period in May, 2013, and that additional maintenance activity was required to address the increased microbiological load. You failed to validate the purified water system after completing the required maintenance activities.

## D. Chemicals & Pharmaceuticals Company - 2017 – FDA

**1. Failure to validate and monitor the water purification system to ensure that water is of appropriate quality and suitable for its intended use.**

During the inspection, our investigators found that your water purification system was not adequately monitored and controlled. Because you use water as a drug component and for cleaning your facility and equipment, these failures pose significant risk to the safety of your drugs.

*Source water*

You failed to test the source water for your water system. The source water emanates from a nearby river and passes through farmland, where it is subject to agricultural runoff and animal waste, before reaching your facility. Your firm stores the source water in an tank that has a large facing hole that is open to the environment. Your storage method does not protect your water from dirt and other contaminants, or from the ingress and proliferation of pests and objectionable organisms.

*Sanitization and validation*

You did not follow your own sanitization procedures for your water system. Your procedures specify sanitization at, yet our investigators identified instances where you sanitized for as little as 10 minutes without justification.

*Testing*

Our investigators found that you were aware that the total aerobic microbial counts (TAMC) for all in-process water samples had exceeded your limit of colony forming units (cfu)/mL for multiple months. You failed to investigate these deviations.

## E. Global Pharmaceutical Company - 2016 – FDA Inspection

**Failure to adequately investigate critical deviations and implement corrective and preventive actions.**

*Microbial contamination in water systems .*

From April 20, 2014, to February 17, 2015, you investigated at least 25 breaches of the alert level or action level for microbial contamination in your water system loops. You used water produced from this system to manufacture API. Of note, you identified a waterborne organism known to contribute to biofilm formation in water systems, in several of your alert-level and action-level investigations.

Your investigations failed to adequately establish root causes. In 16 of the 25 investigations, you concluded that the root cause was sampling error but had no supporting evidence. You did not determine a root cause in the remaining nine investigations. Our inspection also found that you were not sanitizing the water system loops, as required in your procedure.

## F. Cosmetic Company - 2016 – FDA Inspection

**Water System Failures:**

Your firm failed to maintain your reverse osmosis (RO) water system for topical drug products. During the inspection, our investigators observed leakage in the RO water system. Your Director of Operations told our investigators that your RO water system had been leaking for more than six months since August 2014. No action was taken to repair the leaks during that entire time.

Our investigators also determined that your monitoring, inspecting, and repair of the RO water system was inadequate in ensuring that it was maintained in a validated state. Beyond the failure to maintain your RO system from January 8, 2014, through October 8, 2014, microbiological test results from water sampled at the RO were TNTC on several occasions. Without justification, you discontinued sampling at the RO that yielded these results. We note that the finished product lots that you rejected in 2013 for microbial contamination included gross contamination with Pseudomonas aeruginosa, a microorganism commonly found in water.

## Presentation Overview

- Being constantly audit ready, reduces the disruption that an audit has on an organization.
- Vague procedures invite variable execution and variable test results.
- Tour with your users, and constantly consult with them.

THANK YOU

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