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Quality by Design and Data Integrity in Aseptic Pharma

Understanding GMP & FDA requirements and becoming compliant

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Agenda

- Quality by Design Concept
- What is *Data Integrity*?
- Standard references
- Ethic approach
- Particle Measuring Systems' Solution

Sterile products

Two categories of sterile products:

- *those that can be sterilized in final container (terminally sterilized)*
- *those that cannot be terminally sterilized and must be aseptically prepared*

Sterile product

- ***Non parenteral***
  - Eyes drops
  - Topicals (creams, lotions, ointments, gauze)
  - Irrigations solutions

- ***Parenteral***
  - Ampoules
  - Vials
  - Bottles
  - Syringes
  - Bags

Aseptic Processing - Overview

Aseptic processing

- Objective is to maintain the sterility of a product, assembled from sterile components
- Operating conditions so as to prevent microbial contamination

Aseptic Processing areas/cleanrooms

1. Traditional cleanroom production
   - Complete presence/interaction of people in grade A. The production must be done under grade A and grade A must be installed in grade B surrounding environment.
2. RABs open systems
   - Physical separation of people from grade A but grade A air exhausted in grade B. The RABs must be installed in grade B surrounding environment.
3. cRABs close systems
   - Physical separation of people from grade A and grade A air recirculation inside cRABs. The cRABs must be installed in grade B surrounding environment.
4. Isolator systems
   - Complete physical separation of people from grade A and grade A air recirculation inside isolator. The isolator can be installed in grade C environment

Aseptic Processing areas/cleanrooms

All 4 cleanroom conditions are declared and validated as Grade A

- But in reality only cleanroom (isolator) n°4 is a real grade A
- Cleanroom 1 is not a Grade A microbiologically because operator presence

Quality by Design (QbD) and microbiology

Definitions:

Quality – "the suitability of either a drug substance or drug product for its intended use" – ICH Q8

Quality by design – uses process understanding to deliver product with the desired critical quality attributes.

Process understanding – in-depth knowledge of factors affecting a product's critical quality attributes (see PAT guidance).

Design Space – "the multidimensional combination and interaction of input variables and process parameters…. demonstrated to provide assurance of quality" – ICH Q8

What is Quality by Design (QbD)?

Quality by Design is:

- A systems for designing, analysis, and controlling manufacturing through timely measurements (i.e. during processing) of *critical quality parameters* (CQP) and performance attributes of raw and in-process materials and processes (CPP) with the goal of ensuring final product quality.

- It is important to note that the term analytical in QbD is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

Quality by Design steps

- For all aseptic production processes we need to identify the chemical, physical and microbiological critical quality attributes (CQA) and critical process parameters (CPP) using risk analysis (FMEA, FMECA) tools.
- For the CQA and CPP identified we need to define the best monitoring /controls technology and instrument.

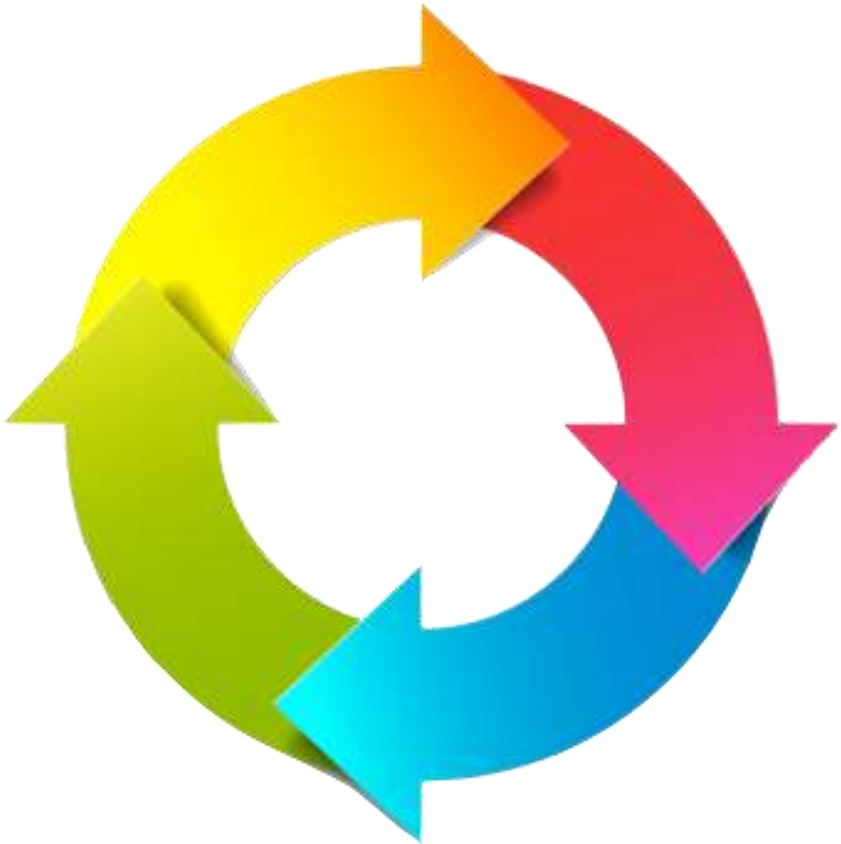
FDA Initiatives - Innovation

Beginning in 2002, FDA recognized the need for pharma industry to be **more innovative**; therefore, launched:

- **Critical Path Initiative**
- **Pharmaceutical Quality for the 21st Century – A Risk Based Approach**
- **Quality by Design (QbD)**
- **Process Analytical Technology (PAT)**

Goal of all is to modernize and improve quality of pharmaceutical manufacturing processes – encourage industry to implement risk-based, continuous, real time quality assurance

The Data Integrity Concept



Data Integrity refers to maintaining and assuring the accuracy and consistency of data over its entire product life-cycle.

Data Integrity in Pharma industries

Data Integrity is not a new requirement

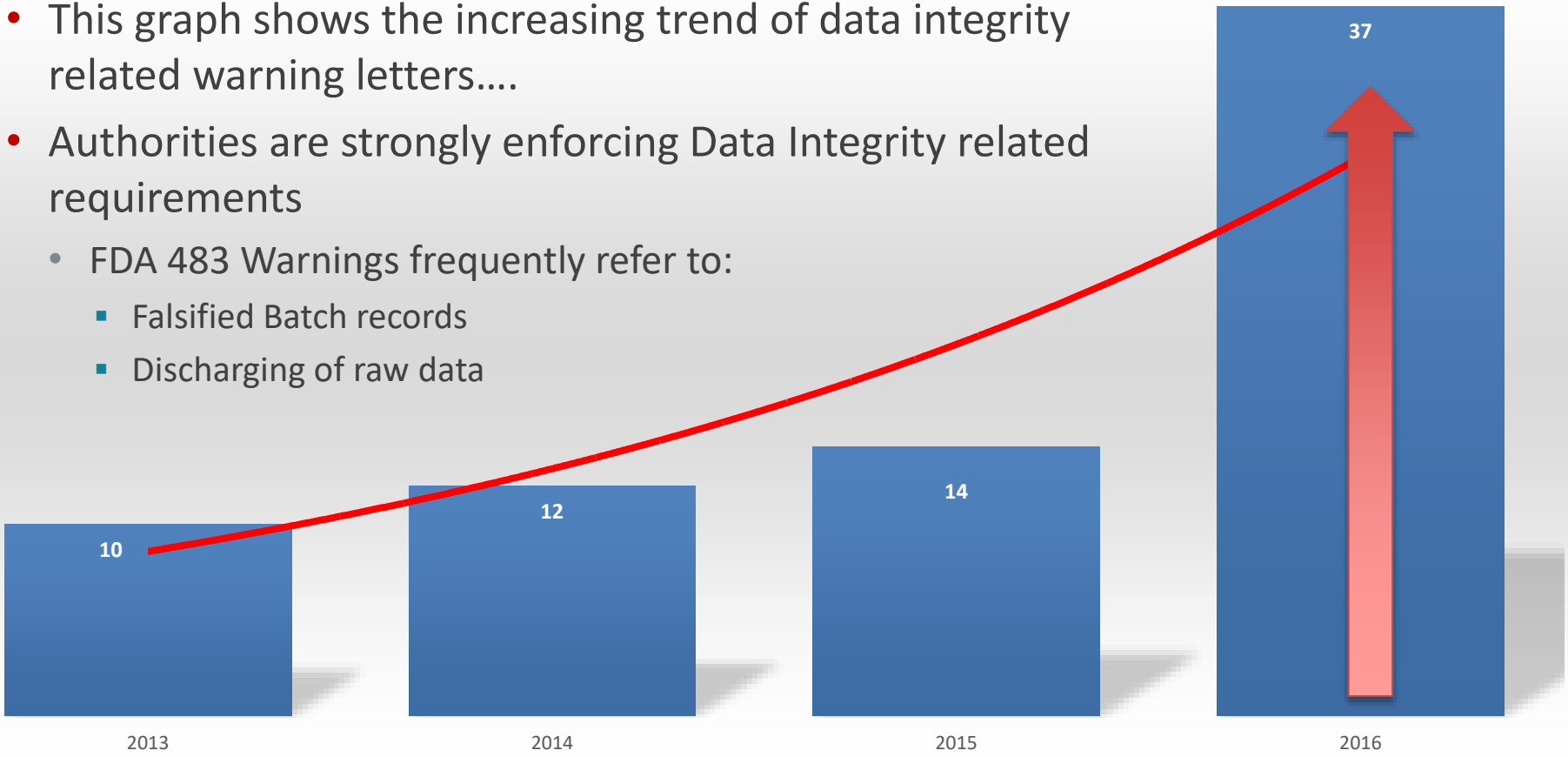
- UK “Orange Guide” 1971:
  - Copies from master records to avoids transcription errors
  - Initials of people who perform each activities
  - Record of the history of each batch, from supply chain to the final package.
- EU GMP 1989
  - Data alteration or correction requires signature, reason and permit original data reading
  - Records must be completed at the time the action is taken
  - Name of person who performed and checked the action

The Data Integrity Today

- Over the last few years several FDA Warning letters (483) have been issued for Data Integrity deficiencies in the Pharma industry.
- In 2015, more than 50% of MHRA warning letters involved data integrity lapses.
- Inspector are actively trained about Data Integrity requirements control.

Global Warning Letters Citing Data Integrity

- This graph shows the increasing trend of data integrity related warning letters….
- Authorities are strongly enforcing Data Integrity related requirements
  - FDA 483 Warnings frequently refer to:
    - Falsified Batch records
    - Discharging of raw data



Data Integrity Today

- Deep knowledge and understanding of the most recent Data Integrity related standards, guides, and regulations is an essential step to be…

- The Data Integrity Compliance aim is to:
  - Increase Product Quality
  - Reduce product defects and costs
  - Increase regulator confidence
  - Real-time release
  - Increase brand reputation
  - Increase process control

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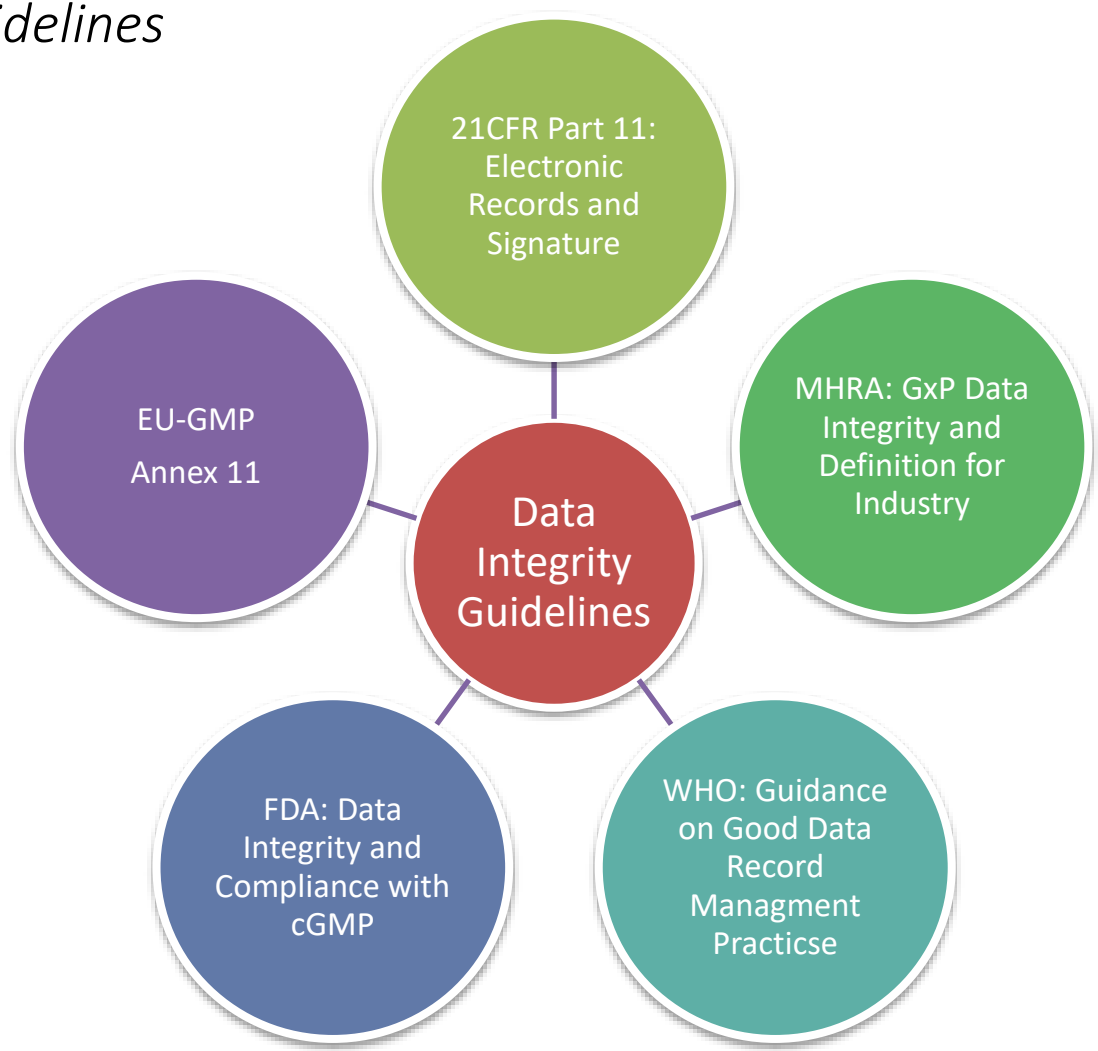
Standards & Guidelines References

Standard and Guidelines

Manufacturers of finished drug products for clinical trials, bioequivalence studies, and commercial distribution, Laboratories, Contract Manufacturing, Suppliers…… etc. must refer to the actual Data Integrity related guidelines in order to guarantee compliance data management.



Data Integrity – 21 CFR Part 11

21CFR Part 11

Code of Federal Requirements

21CFR Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved or transmitted under requirements set in agency regulations.

Electronic records/signatures that meet the requirement of part 11 may be used in lieu of paper records

21CFR Part 11

Code of Federal Requirements

21CFR Part 11 represent the most used and required standard for a correct data management.

Main requirements include, but are not limited to:

- General Provisions
- Electronic records
- Electronic Signatures

Validation

Computerized system must be validated to ensure the data accuracy, reliability and consistency.

System must discern invalid or altered records.

- Computerized system must generate an accurate, complete and human-readable copy of the records.
- Access limitation using ID / Password combination
- The determination of who develops, maintains, or uses electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks, is essential to guarantee the data integrity.

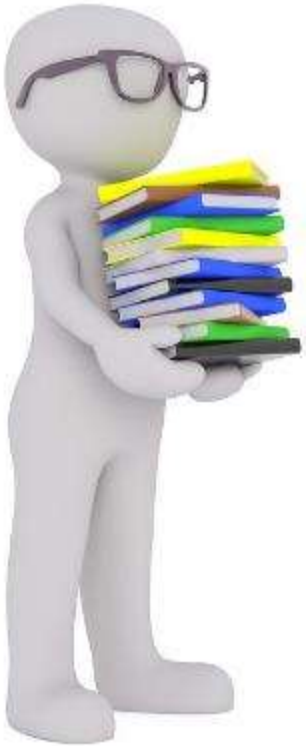
Data Integrity and Compliance With CGMP Guidance for Industry

- Data Integrity and Compliance with CGMP Guidance for the Industry
- Is currently a DRAFT Guidance
- Intended to clarify the role of data integrity in current good manufacturing practice CGMP.
- Expects data to accurate and reliable
- Does not establish legally enforceable responsibilities. Describes the Agency's current thinking. Is suggested and recommend but not required.

Eudralex GMP Annex 11

- In the European Union (EU), EudraLex is the collection of rules and regulations governing medicinal products (for human use as well as for veterinary use).
- Annex 11 is part of the European GMP Guidelines and defines the terms of reference for computerized systems used by organizations in the pharmaceutical industry.
- It's important to note that Annex 11 is not a regulation, like the FDA 21 CFR Part 11 rule

Eudralex GMP Annex 11



- The guidelines set forth by the Commission of the European Committees are not too distant from their US counterpart created by the FDA (21 CFR Part 11).

- Among other things, Annex 11 defines the criteria under which electronic records and electronic signatures are considered to be managed.

Ethic Approach

Ethic Approach

From the PDA Journal:

- *Prevention*
  - The prevention of data integrity breaches can be addressed with three primary elements: Personnel and Training, a Validation Program, and Security.
- Company standards of ethical conduct are defined to be followed, assuring that each employee acts with integrity in the execution of their work.
- Each employee is responsible for the validity and integrity of their data and documentation, whether it is a paper-based or electronic system.

PDA®
Parenteral Drug Association

Ethic Approach

- Avoid potential breaches of ethical behavior such as (but not limited to) the following:
  - Improper data manipulation
  - Adjustment of time clocks
  - Backdating of information
  - Creating records after the fact or without actually executing the procedure
  - Excluding adverse information
  - Sharing of passwords
  - Discarding or destroying original records

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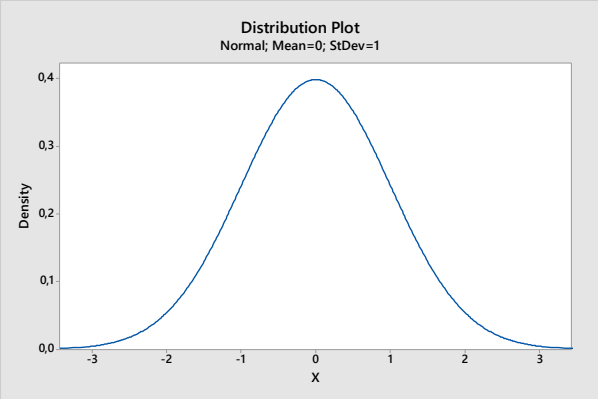
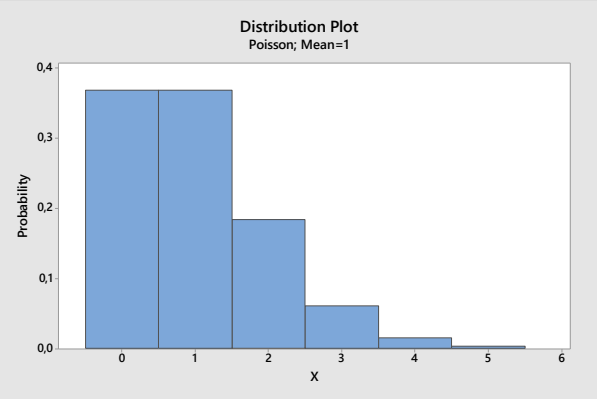
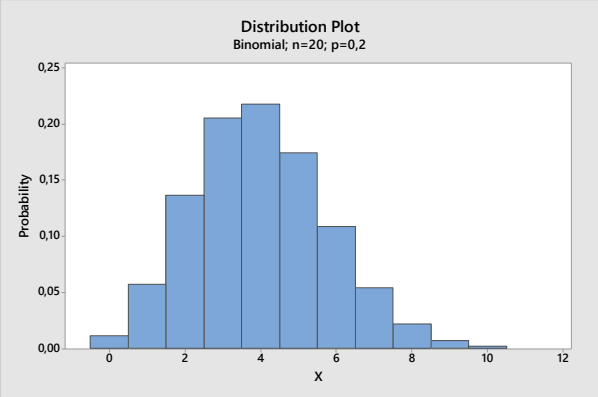
EM Action and Alert Limits & Trends
- Statistical Overview -

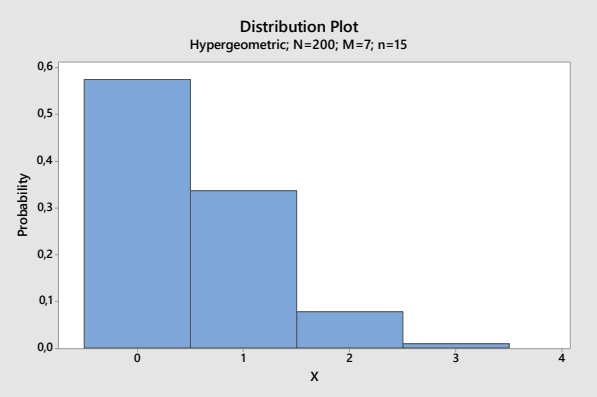
Types of Data

Which kind of statistical distribution is best for your microbiological and particle data?



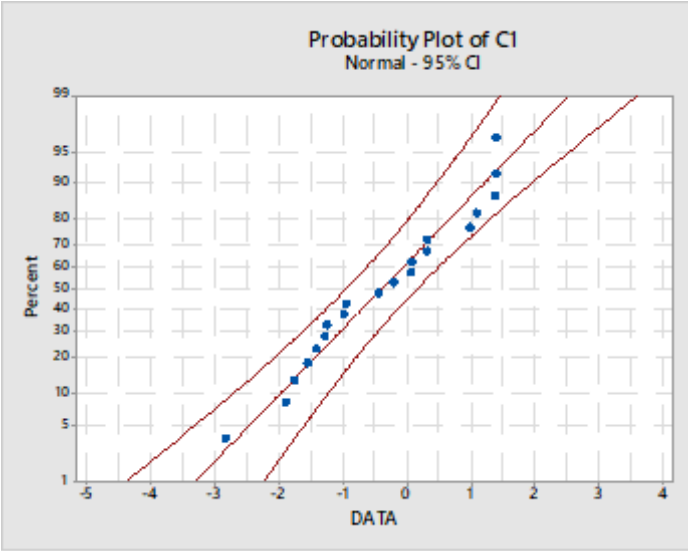






Confidence Interval and Level

- In **Environmental Monitoring (EM)** and also Quality Control, the data derives from sampling.
- The **Confidence Interval,** a range of values derived from sample statistics, is likely to contain the value of an unknown population parameter.
- The **Confidence Level** represents the percentage of intervals that would include the population parameter if you took samples from the same population again and again.



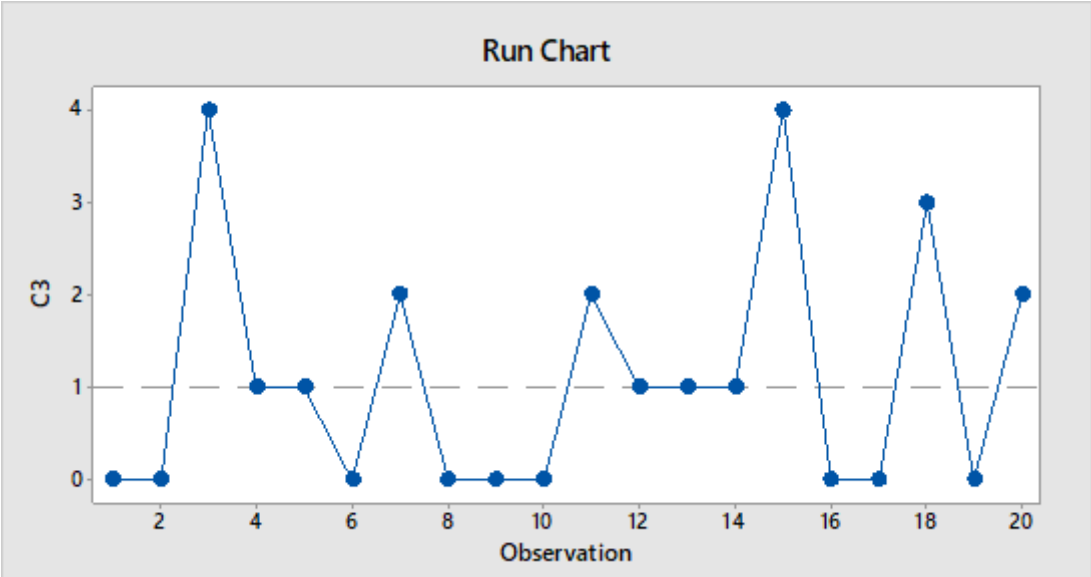
A **Probability Plot** can be useful to evaluate which kind of probability distribution the data follows with a prefixed confidence level.

Statistical Tools

- **Define** which kind of distribution is best in order to choose the right tools to analyse the environmental data.
- **Mean and standard deviation** can be the right tools **only** if the data follows the normal distribution.
- **Non-normal statistic tools** must be used for all other types of distributions.
- Otherwise, in some cases, it can be useful to **transform the non-normal data into normal** data applying advanced statistical techniques.

Run Charts

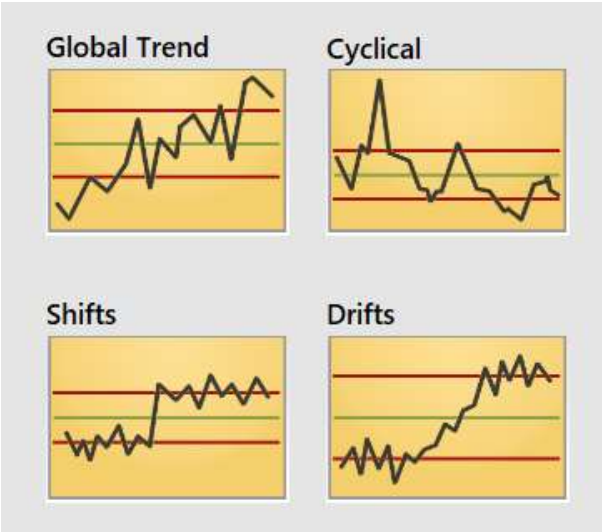
- A **Run Chart** is a graph that displays EM data observed in a time sequence.
- It's useful to look for **patterns or trends** in your data that indicate the presence of special-cause variation.

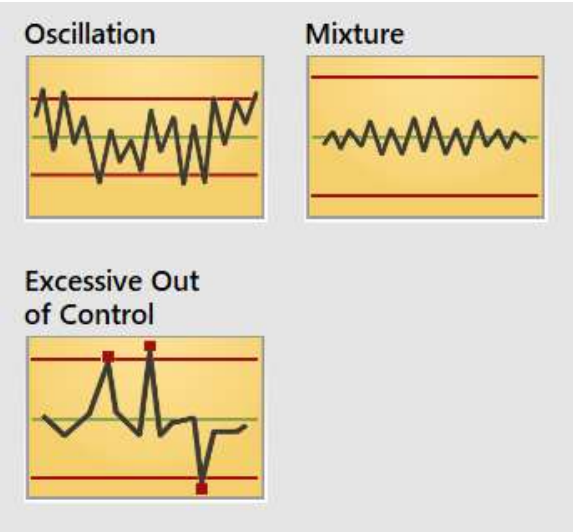


Patterns and Trends

- Each **pattern or trend** can be the effect of a problem that must be investigated in order to define if that data must be excluded from the limits calculation.

- Several **p-value tests** can be run to identify the following defects:

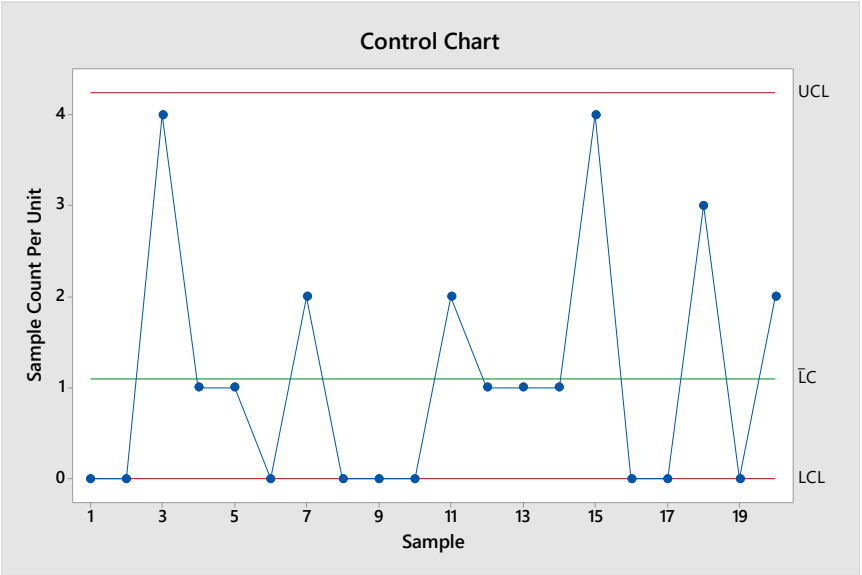




Control Charts

- **Control Charts** (also known as Shewhart charts), are statistical tools used to evaluate if a process is in a state of statistical control.

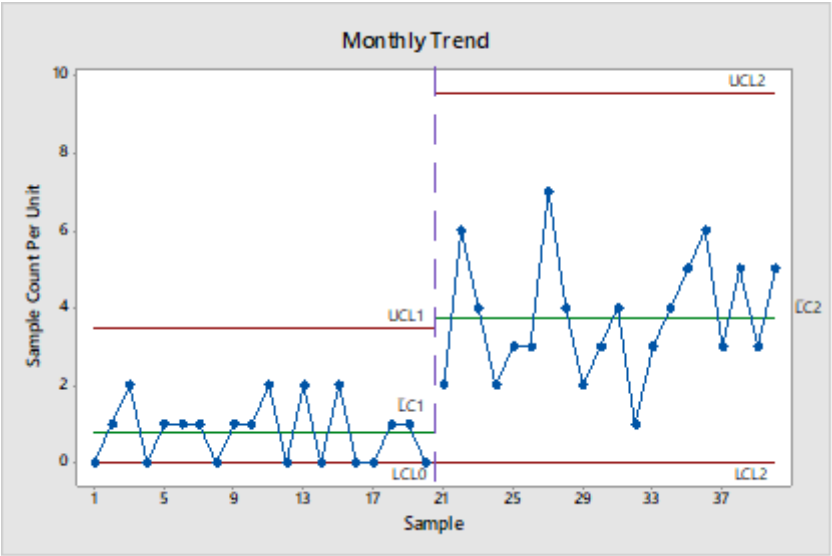
- Choosing the right chart for the probability distribution, followed by the sampled data, allows for the possible calculation of **Action and Alarm limits**.



Periodic Trend Analysis

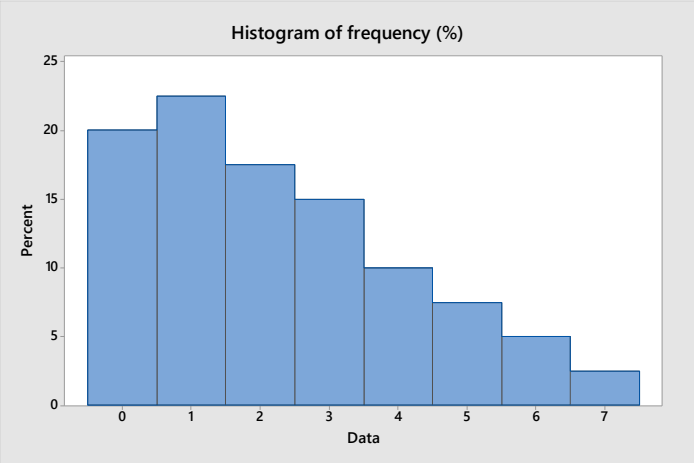
- **Run Charts** and **Control Charts** are also useful to periodically analyze the total particle data and microbiological data

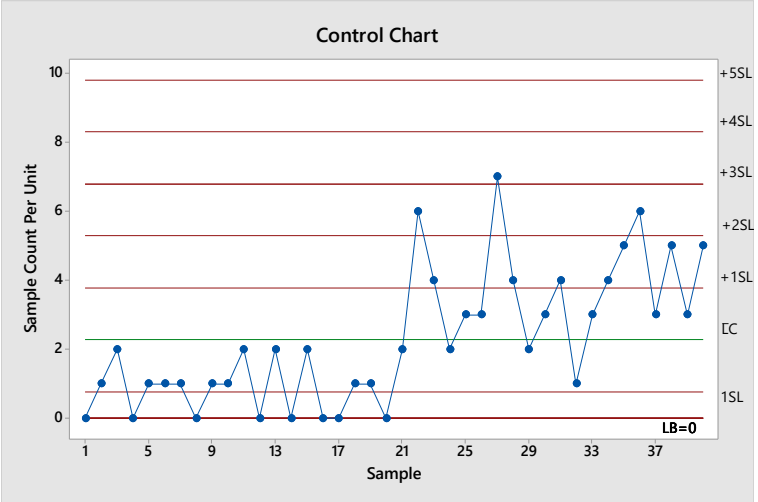
- Comparing sampling between **two or more periods** can highlight if the environment is going under a modification or drift towards a limit.



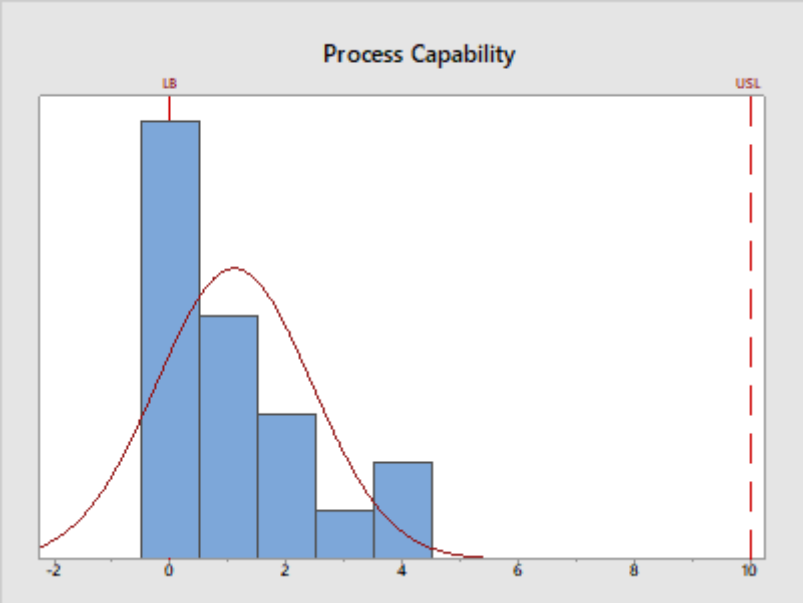
Periodic Trend Analysis

Combining **Histograms of frequency** with **Control Charts** can help to understand how the data are distributed.





Process Capability



- The **environmental status** is the measurable output to a unique combination of tools, materials, methods and people engaged in production, and each factor has a inherent statistical variability.
- If with control charts analysis the process is marked as "**in statistical control**", the **overall capability** of the environment status is a measurable property.
- The **capability index** refers to the ability of a process to meet predefined specifications.

Conclusion

THE KNOWLEDGE OF STATISTICS IS NOT ENOUGH TO DEFINE ALERT AND ACTION LIMITS.

THE BEST SOLUTION IS THE COMBINATION OF STATISTICS KNOWLEDGE AND PRODUCTION PROCESSES.

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Particle Measuring Systems' Solution

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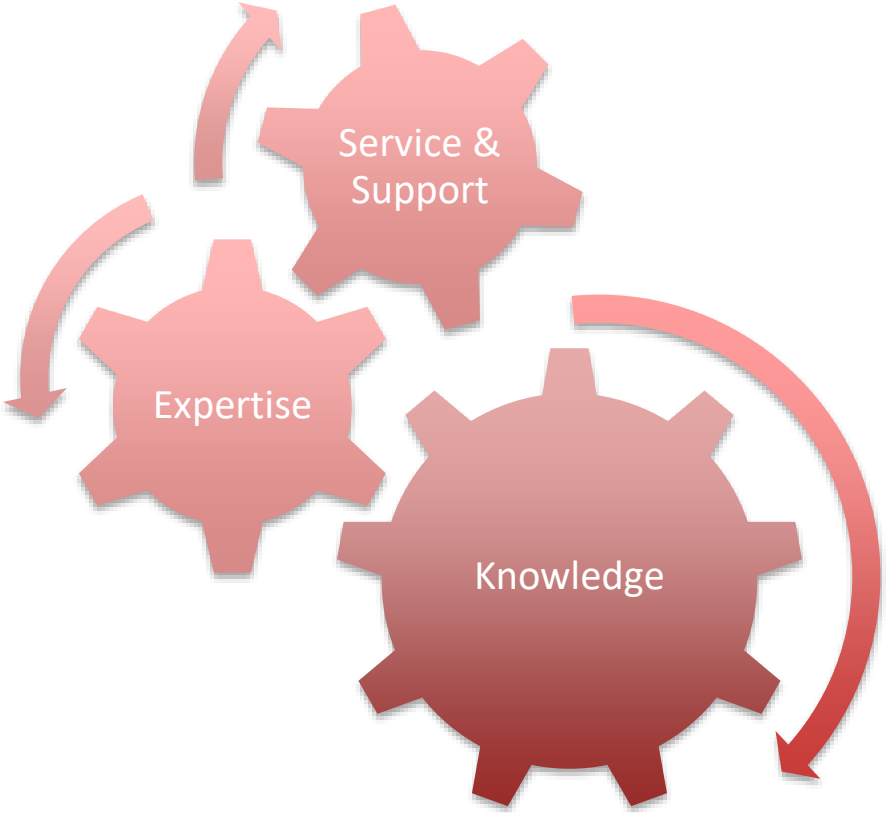


Based on a solid mechanism…

Particle Measuring Systems – Portable units

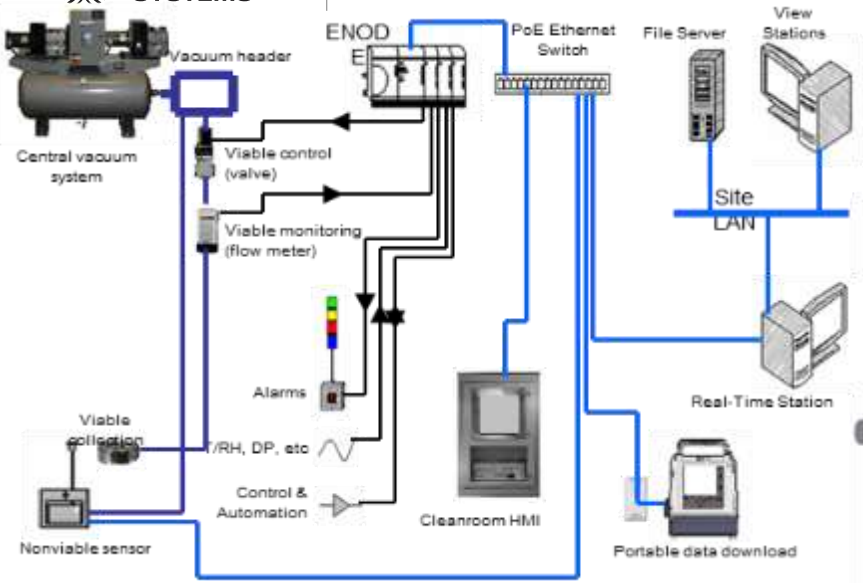
- Lasair III Particle Counter and MiniCapt Mobile Microbial Air Sampler
- Restricted access
  - User and operator log in
  - Multilevel access
  - Operator ID
- Data 21 CFR part 11 in the instruments
  - Unchangeable data base
  - Capability for creation of hardcopy via printers
- GAMP 5 Category 3 software: Non-configured products

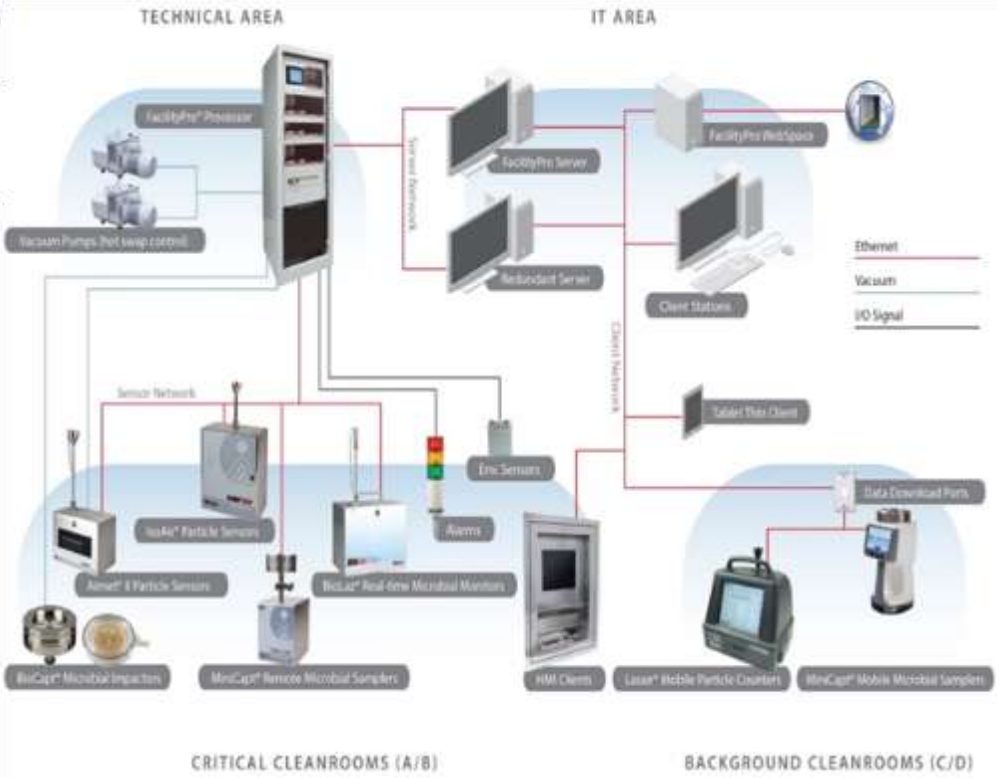
  Dedicated printer to generate un-editable report which in compliance with Data Integrity requirement

  Three-layer authority architecture in compliance with the security management requirement of GAMP 5

Compliance Statement for Lasair® III Particle Counter to 21CFR11 "Electronic Records & Electronic Signatures"

The PMS approach to Data Integrity

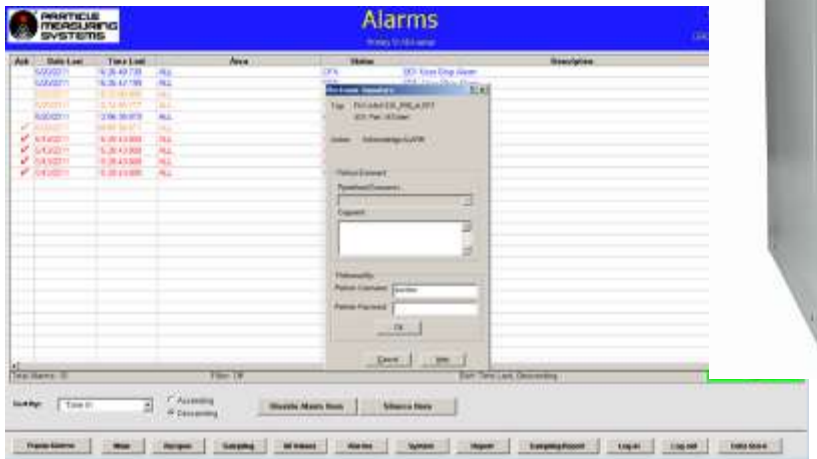




Particle Measuring Systems – FMS systems

- Tracking for all changes
  - Multilevel user, operator administrator
  - Assignable access

- Data Integrity
  - 21 CFR Part 11 database
  - Sensor driven time stamps
  - Data Back up and recovery.
    - Redundant vacuum systems
    - Redundant SCADA
    - Routine backups



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Conclusion

Conclusion

- It is imperative that everyone in the company understands they are ultimately responsible for data integrity.
- Data Integrity is a significant component of the Quality Management System,
- Inspectors around the world have made it very clear that good intentions are no defense against compromised data.
- Pharmaceutical industry must strongly consider any preventive or corrective action to improve the product quality through enhanced data integrity and ethic behavior.

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