

BAYBIO

geneacres14

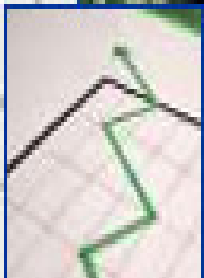
Building Successful Life Science Facilities

September 21, 2006  
San Mateo Marriott

# Maintenance Track

**DC** ENGINEERING  
CONSULTING, INC.

Project management services  
for the high tech and biotech  
construction industries.



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# The Presentation



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**Introduction**      **Bob D'Elia – DC-Engineering**

**Discussion 1**      **What type of Maintenance Department do I need?**  
**By: James Bennett – Genentech**

**Discussion 2**      **Should we fear an FDA Audit?**  
**By: David O'Connell – DC-Engineering**

**Discussion 3**      **Auditing (Metrics) to assure compliance**  
**By: John Zimmerman – Nectar**

**Questions**      **ALL**

# Why Do We Comply?



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- Drug - Identity, Strength, Quality, Purity, Efficacy, Safety – **Every Time**
- No 100% End Product Testing
- Systems in Place to Assure...
- Preventive Maintenance is one of those systems

# The Audit:



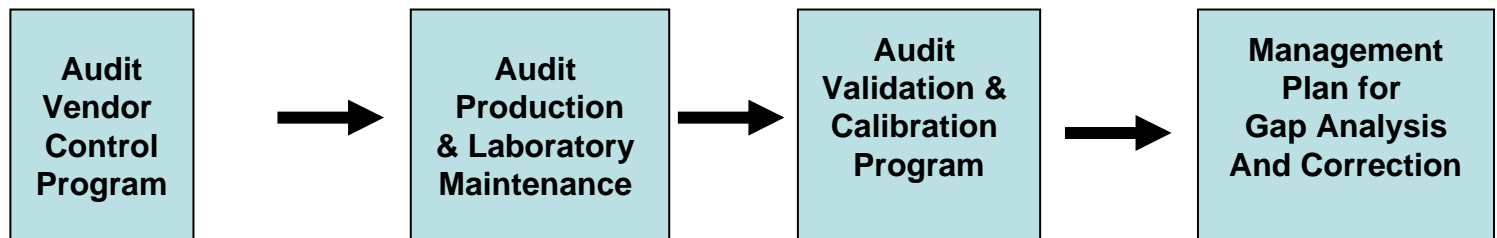
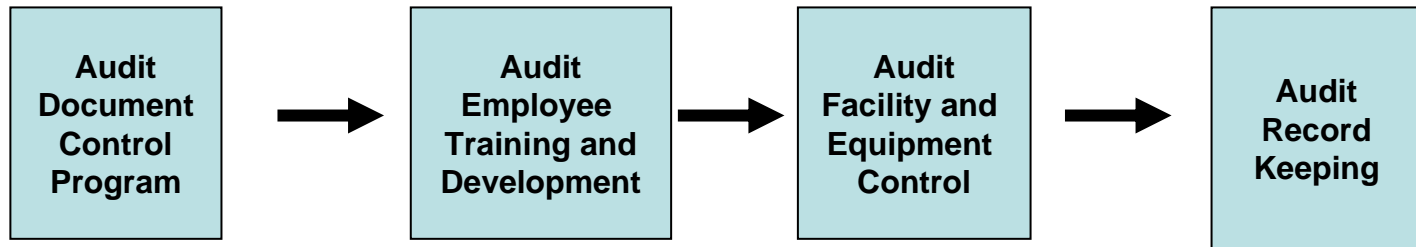
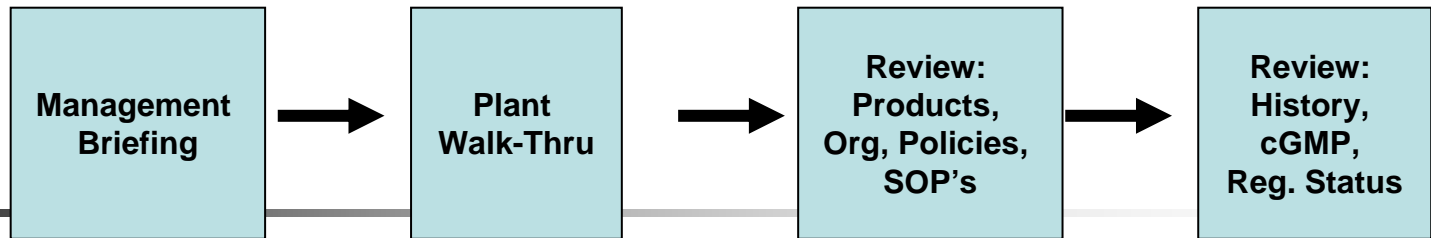
The following is a list of systems upon which the FDA bases their inspections:

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1. Quality System.
2. Facilities and Equipment Systems.
  - a. **Building and facilities along with maintenance.**
  - b. Equipment qualifications (installation and operations); equipment calibration and preventive maintenance; and cleaning and validation of cleaning processes as appropriate.
  - c. Utilities that are not intended to be incorporated into the product such as HVAC, compressed gases, steam and water systems.
3. Materials System.
4. Production System.
5. Packaging and Labeling System.
6. Laboratory Control System.

An inspection consists of an audit of two or more systems with mandatory coverage of the Quality System. Selecting unique functions within the system is at the discretion of the lead investigator. The cGMP Maintenance Inspection Audit shall include:

# The Audit Process:



# An Actual 483:

Dear Dr. \_\_\_\_\_:

...The United States Food & Drug Administration has completed its review of the September 18-21, 2000, inspection of your active pharmaceutical ingredient (API) manufacturing facility in Hyderabad, India, by FDA Investigator Ted L. Anderson and Chemist Michele L. Obert. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of APIs. The deviations were presented to you on an **FDA Form 483 Inspectional Observations** at the close of the inspection. These deviations cause the API to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice. No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act:

**(Failure to establish and maintain schedules and maintenance activities for the adjustment, cleaning, and other maintenance of manufacturing equipment [21 CFR 820.70(g)(I)].) Equipment was not properly maintained. Although your responses describe corrective actions for each of the examples listed on the FDA 483, you failed to state how you will monitor all equipment (e.g. a preventative maintenance plan) in the future, and how you will make sure that maintenance is accomplished in a timely manner.**

Food and Drug Administration  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, MD 20855



## Title: Specifically, What Type of Maintenance Department Do I Need?

Name: James Bennett

Title: Senior Facilities Coordinator

Event: Gene Acres

Date: 21 Sep 06

# Why Do I Need A Maintenance Plan?

◆ **“Any buildings used in the manufacture, processing, packing or holding of a drug product shall be maintained in a good state of repair.”.**

- Facilities that practice the manufacturing of goods for human consumptions must be approved and regulated under Food Drug Administration (FDA)
- “PART 210 – Current Good Manufacturing (cGMP) Practice In Manufacturing, Processing, Packaging, Or Holding Of Drugs & Finished Pharmaceuticals.”

**“cGMP Preventive Maintenance Inspection Audit” is outlined in Part 211 / Sub-Part “C” – Buildings & Facilities...Section 211.58: Maintenance.**

# So What Type Of Maintenance Dept?

## ◆ Purpose And Function.

- Consistency.
- Dependability.
- Effectiveness.
- Redundancy.

## ◆ Categories Department Response

- Reactive Maintenance
- Preventative Maintenance (PM)
- Predictive Maintenance (PdM)
- Reliability-Centered Maintenance (RCM)

# Department's Mission Statement

## ◆ Mission Statement For Department

- Identify the scope for the department and objective.
- Interaction with other departments and groups to provide communication of department's intent.
- Identify the customer focus group within the statement summary
- *“Maintenance, operation and repair of facilities, grounds and equipment to all company employees...”*

# What Type Of Maintenance Dept? – cont.

## ◆ Staffing.

- Most FDA regulated will require 24/7 staffing or response program.
- Determination if staff will be “in-house” or outsourced
- Dispatch or Call Center organization.
- Specialty contractors established with “blanket P/O’s” for emergency calls and 24/7 response to assist maintenance department.

# What Type Of Maintenance Dept? – cont

## ◆ Documentation.

- Equipment is validated at time of initial start up.
- Standard Operational Procedures (SOP)'s on the proper guidelines for equipment reliability and dependability along with the maintenance requirements.
- Complete training to prove who is authorized and how the training has been developed to personnel to perform maintenance and needed repairs to all equipment.
- Complete records maintained for all maintenance and repairs performed to all equipment.

# The Challenge

## ◆ Staffing.

- Finding and retaining qualified personnel to maintain and operate facilities equipment.
- Establishing a (24/7) operational organization
- Modifications to training requirements and document control.
- Effectively managing the routine (planned) versus the respond (un-planned)

## ◆ Funding.

- Approved funding for the organization that usually is considered “overhead” (or) “below the line” expense.
- Company long range plan defined to determine the expected life of equipment asset values.

## ◆ Department / Organizational Collaboration.

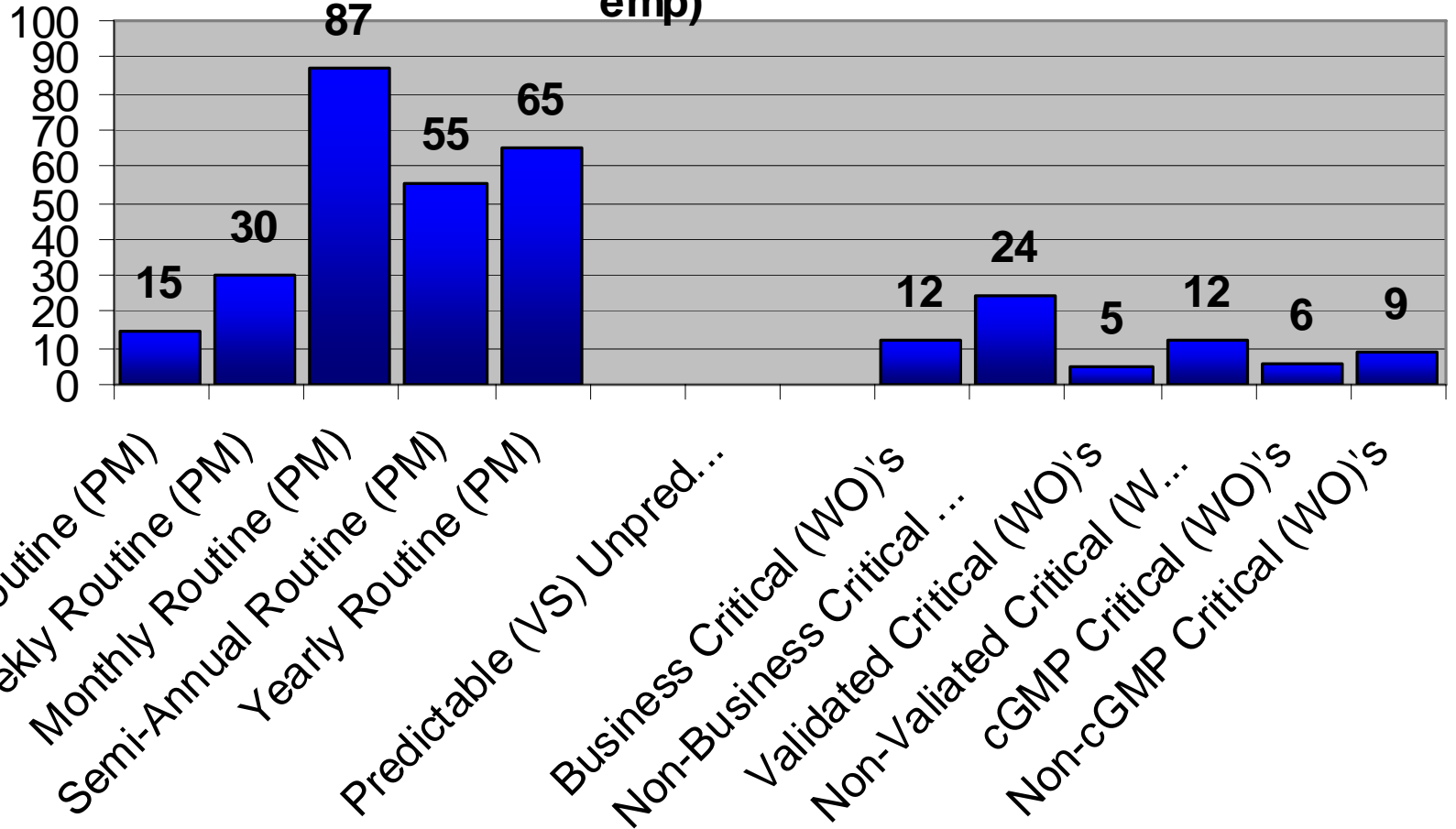
- All departments working together as one common goal.
- Communication among department leaders to effectively join “Mission Statements”.
- Engineering & Users effectively communicating and planning the intent use for operations at the time of preliminary development.

# Conclusion

- ◆ **The maintenance department's main mission is to maintain, repair and operate equipment to where the customers are not effective in their daily operations. In the FDA regulated facility, cGMP, these demands are predetermined for equipment set ranges and standards and require specific documentation to prove compliance for consistency, dependability, effectiveness and redundancy if needed. In order to achieve this, the department's greatest asset are the employees and vendor's invested in this operation. Training is required to qualify the personnel tasked for specific scopes and maintaining all documentation. Other departments within the company's infrastructure should develop strong communication skills to relay and share the company's mission statement. With all groups working as a whole – the achievement of maintaining a FDA regulated cGMP Facilities per Part 211 / Sub-Part "C" has be accomplished.**

# Staffing: Planned (vs) Un-Planned

Maintenance Department Work Load (IE: Campus Size = 2,000 emp)



# Maintenance Mechanics Scheduling

Mechanica Shift Schedules							
	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
<b>Day Shift (6 am - 4 pm)</b>	Assistant Chief Mechanic 1 Mechanic 2		Assistant Chief Mechanic 3 Mechanic 4				
<b>Swing Shift (12 noon - 10 pm)</b>	Mechanic 5 Mechanic 6 Mechanic 7		Mechanic 8 Mechanic 9 Mechanic 10				
<b>Grave Shift (9 pm - 7 am)</b>	Mechanic 11 Mechanic 12 Mechanic 13			Mechanic 14 Mechanic 15 Mechanic 16			

# Discussion #2:

**Should we fear an FDA Audit**

**By: David O'Connell**  
**DC Engineering**

# What to Manage?



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- Asset Management
- Work Management
- Human Asset Management
- Materials Management
- Purchasing
- Compliance with Government Regulations
- Validation
- Calibration

# Asset Management Set-up

**The equipment shall be identified by the following:**

- Equipment types categorization, numbering and description
- Model number, serial number
- Equipment Location
- Cost centers
- Department
- Components

**Do NOT let other departments control your assets!**

# Work Management

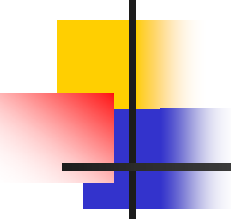


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## **Work Management**

The validation process is used to confirm that a system, as configured for a process, operates as designed and has built-in features and capabilities to ensure that the data entered and stored receives sufficient protection from unauthorized alteration. Some of the most important data concerns current Good Manufacturing Practices (cGMP), such as maintenance, repair, inspection, calibration and other processes that may affect product quality or safety. Your computerized system should provide a high level of security, stability and configurability to ensure that you can identify, track and protect records that concern cGMP. Validation consists of a set of quality assurance test case documentation to support the development of document policies and procedures related to the implementation and use of your computerized system.

# Computerized Maintenance Mgmt Systems (CMMS) Matrix



Justification	Physical Assets	Information Assets	Key Performance Indicators
<b>Legal Requirement</b>	Reduce risk by ensuring all aspects of compliance, e.g., 21 CFR Part 11	Improved control over processes for better FDA validation support	<p>Validation of process across a large footprint</p> <p>Rapid response to changing regulatory requirements</p>
<b>Revenue Enhancement</b>	Decrease time, cost and risk associated with bringing new products to market	Implementation of best practices in new product introduction process	<p>Increased asset utilization</p> <p>Best practices in maintenance processes</p> <p>Higher operational efficiency</p>
<b>Cost Reduction</b>	Reduce cost of specialized equipment parts	Greater innovation and better use of technology for greater operational efficiency	Reduction in inventory cost for spare parts while maintaining service levels
<b>Risk Mitigation</b>	Provide global visibility and placement of critical, high value spare parts	More emphasis on working smarter, innovation and use of technology for greater operational efficiency	Greater efficiency enterprise wide

# Preventive Maintenance Work Order:



## **At a Minimum, the Preventive Maintenance Work Order Shall Include:**

- Task number scheme with identification and safety requirements
- Task scheduling information (start date, scheduling type, and scheduling frequency)
- Equipment listing
- Task Instruction (as specified by existing procedures and equipment manuals.)
- Required parts and tools
- Reporting and warning information

# Human Asset Management



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- Where Can You Find Maintenance Personnel?
- What Do They Cost?
- What Kind of cGMP Cross Training is Required?
- What Criteria Should Be Used for External Vendors?
- What External Training Classes Are Available?
- What Type of Computer Training is Required?

# Material Management



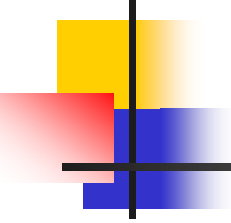
## **Develop basic storeroom operational procedures.**

- Define inventory check out and return procedures
- Stock locations strategies
- Future Bar code practices and implementation strategy
- Staffing requirements

**Inventory integration will be provided in accordance with the SOP and cGMP guidelines.** The following data will be collected and an inventory database developed to meet FDA requirements.

- Inventory database development for Critical Items: Item number, description, type and, location.
- Identification of Items for Product Safety
- Re-order points and quantities will be established along with vendor information and pricing.
- A Physical Inventory of your storeroom will be performed with the help of storeroom clerk: including minor reorganization of inventory if necessary and acceptable to your staff.

# Purchasing

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- **Minimum Re-order Points (MRP) must be Aligned with Maintenance**
  - **Vendor Selection Should include Criteria Establish by Maintenance**
  - **Vendor Audits**
    - **Site Inspections**
    - **Component and Subcomponent Tracking**

# Compliance



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## **“Say What You Do”**

- PM Schedules Established**
- Updated SOPs**

## **“Do What You Say”**

- Training**
- Parts**
- Resources**

## **“Show What You Did”**

- Closeout Documentation**
- Log Sheets**
- Deviation Notifications**

# Validation & Calibration

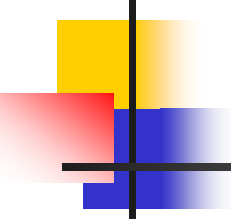


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**Once a System has been Validated the Mechanisms of Keeping it in Compliance are to:**

- Monitor Processes
- Perform Preventative Maintenance
- Calibration Testing

# Pre-Audit Activities

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- **Inspections can Happen at Any Time** (Inspections are Every Other Year, or IND Site Inspection)
  - **Internal Audit Team Meets 4-6 Months Prior to FDA Audit**
  - **External Auditors can Assist in Creating Actionable Items**
  - **Action Items Need to be Monitored and Resolved**



# Title: Maintenance & Metrology in the Biotech Industry

Name: John Zimmerman

Title: Associate Director Maintenance Operations

Event: Gene Acres

Date: 07AUG06

# What is Maintained?

- ◆ **Facility Utilities – plant steam, water chillers, administrative HVAC, electrical systems, etc.**
  - Low guys on the totem pole.
  - Typically gets the least amount of attention and funding.
  - Typically not the most critical of all the operations.
  - Typically NOT Validated.
- ◆ **Process Utilities – Clean Steam / Pure Steam, Clean Room HVAC, Glycol / water chillers, Purified Water Systems, etc.**
  - Receive a high degree of attention from the Mechanic to the Chief Financial Officer.
  - Easy to sell the funding needs to maintain and repair.
  - Very critical to process operations.
  - Always validated.

# What is Maintained cont.

- ◆ **Process / Production Equipment – many types - all facilities have variations of this equipment.**
  - Highest level of attention by all involved.
  - Critical to assuring products are manufactured to spec.
  - Easily funded buy supplying good metrics.
  - Always validated – need to be maintained in a validated state.
  
- ◆ **Laboratory / Analytical Equipment – HPLC, GC/MS, electrophoresis, TOC, etc.**
  - QA / QC testing equipment for product release.
  - Development Analytical Equipment (GLP).
  - Laboratory Utilities.
  
- ◆ **Software / Control Systems – Computerized Maintenance Management Systems, production control systems, etc.**

# The Challenge

- ◆ How do we address these diversified systems in a manner that makes good fiscal sense (Corporate Requirement) and still complies with ALL the regulatory requirements?
- ◆ More and more the industry has decided that cGMP's and EU requirements and ISO standards make good fiscal sense.
  - “Well maintained systems increase productivity and longevity of equipment and systems”.
- ◆ Does this mean we are now validating plant our facility Utilities?
  - NO, we do not have to validate systems to apply the three major rules for compliance.
    - **DOCUMENTATION** – if its' not documented it was not done.
    - **TRAINING** – always a good practice for safety and compliance reasons. A well trained technician is also more efficient.
    - **RECORD KEEPING** – historical data is not only valuable from a compliance perspective but for metric gathering it tells the whole (financial) story. This is also where we get the proof (metrics) that the PM to CM ratio goes down when you apply these standards.

# The Challenge cont.

- ◆ **It has been proven to Corporate Executives that applying a few more dollars up front will have some ROI down the road.**
  - By producing the metrics that indicate the relation of Corrective Maintenance to Preventative Maintenance it becomes evident that the dollars are well spent by applying cGMP's to un-validated equipment.
  - At the same time FDA will audit for those three key items on un-validated systems. They will concede to the approach of not having to validate these systems but they will issue 483's for not having the a robust system that demonstrates control.
- ◆ **Internal Auditing**
  - Today I work to design internal audit programs for my areas of responsibility.
  - By collaborating with QA Auditing I can make sure the level and areas of the audit capture what we know to be the areas of concern for FDA and EU
  - We work together to assure the areas of audit DO include plant utilities that support Biotech manufacturing but have no direct product impact.

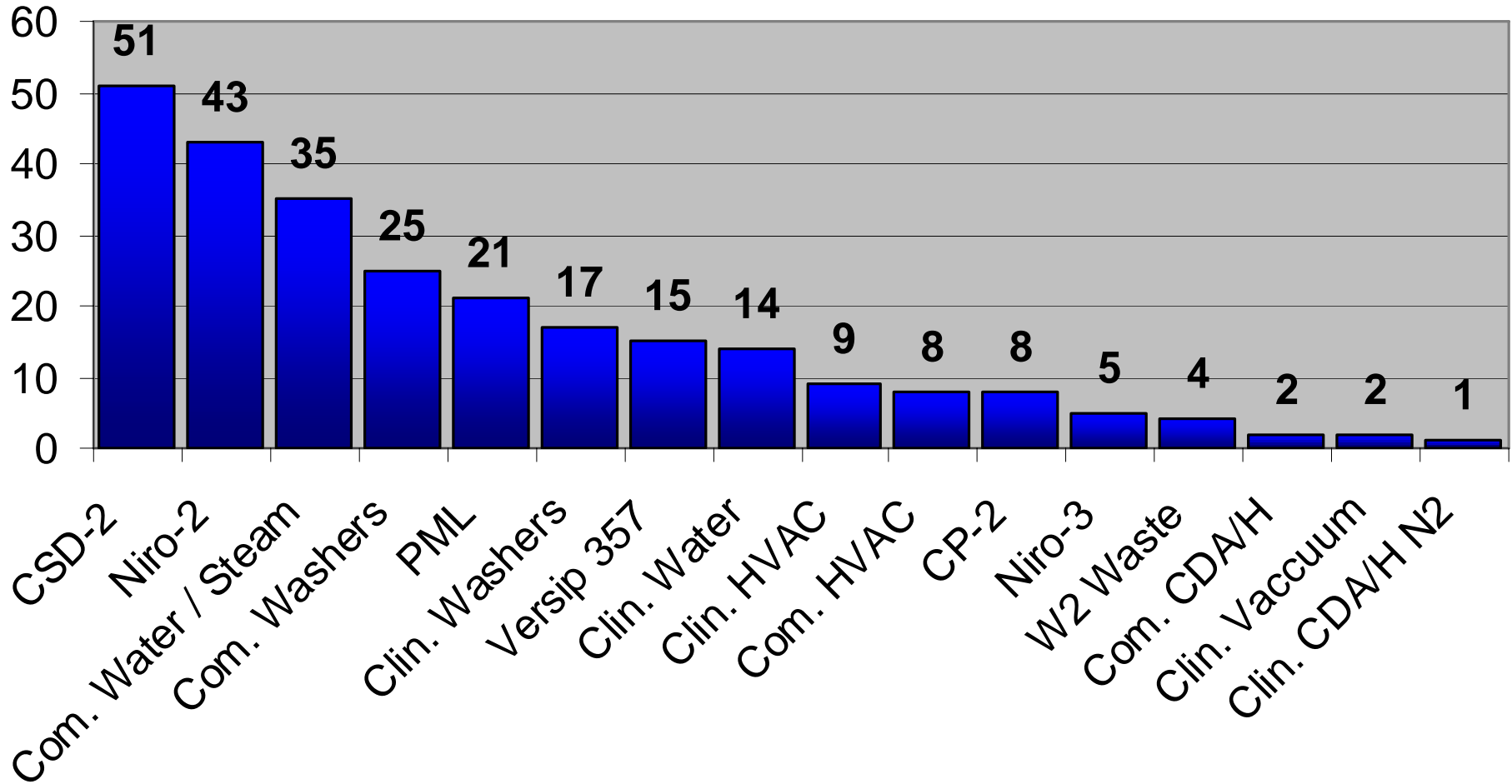
# Conclusion

## ◆ The Importance of Internal Audits

- They support the need and identify the correct “Critical Mass”.
- Critical mass can apply to levels and types of personnel (in-house or contracted trades), levels of spare parts, room to work, etc. These are all the things that we need to justify to corporate executives during the budgeting process.
- They let us know where the deficiencies are – this is the obvious but when a Maintenance or Metrology Dept. Head gets to help design the audit they should be able to use it to their advantage. Better to find potential deficiencies internally than have a regulatory agencies find them.
  - One should not hold back on having a system identified in an internal audit due to that fact they are aware of deficiencies but to open the internal auditors up to that deficiency so all are aware of the pitfalls.
    - This allows the QA and Regulatory depts. To help steer a regulatory audit in the right direction if required.
    - It also supports the required “fixes” to be approved and implemented approved because they re usually due to lack of human resources or parts which require funding. You can watch the money fly when an audit defines the need for financial resources.

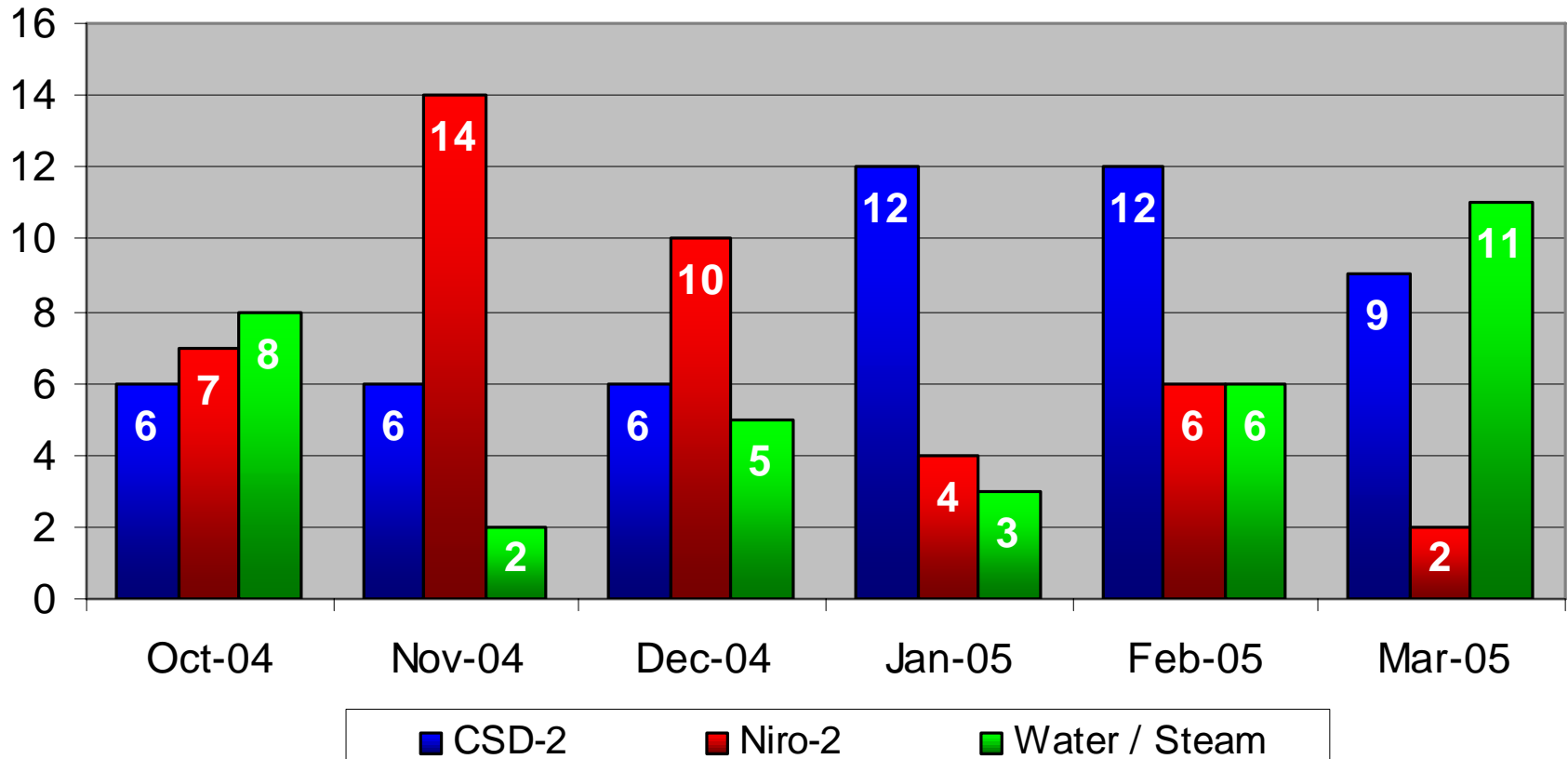
# Sample Metrics

## Total CMs per System

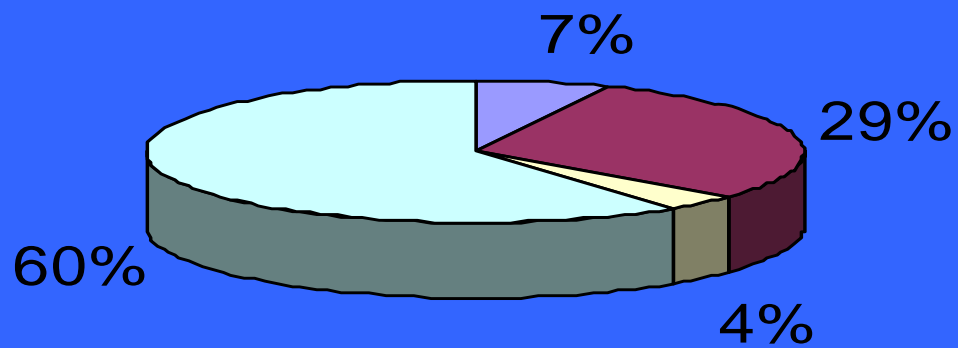


# CM Break Down by Most Occurrences

## Break Down of Systems with Highest CMs per Month

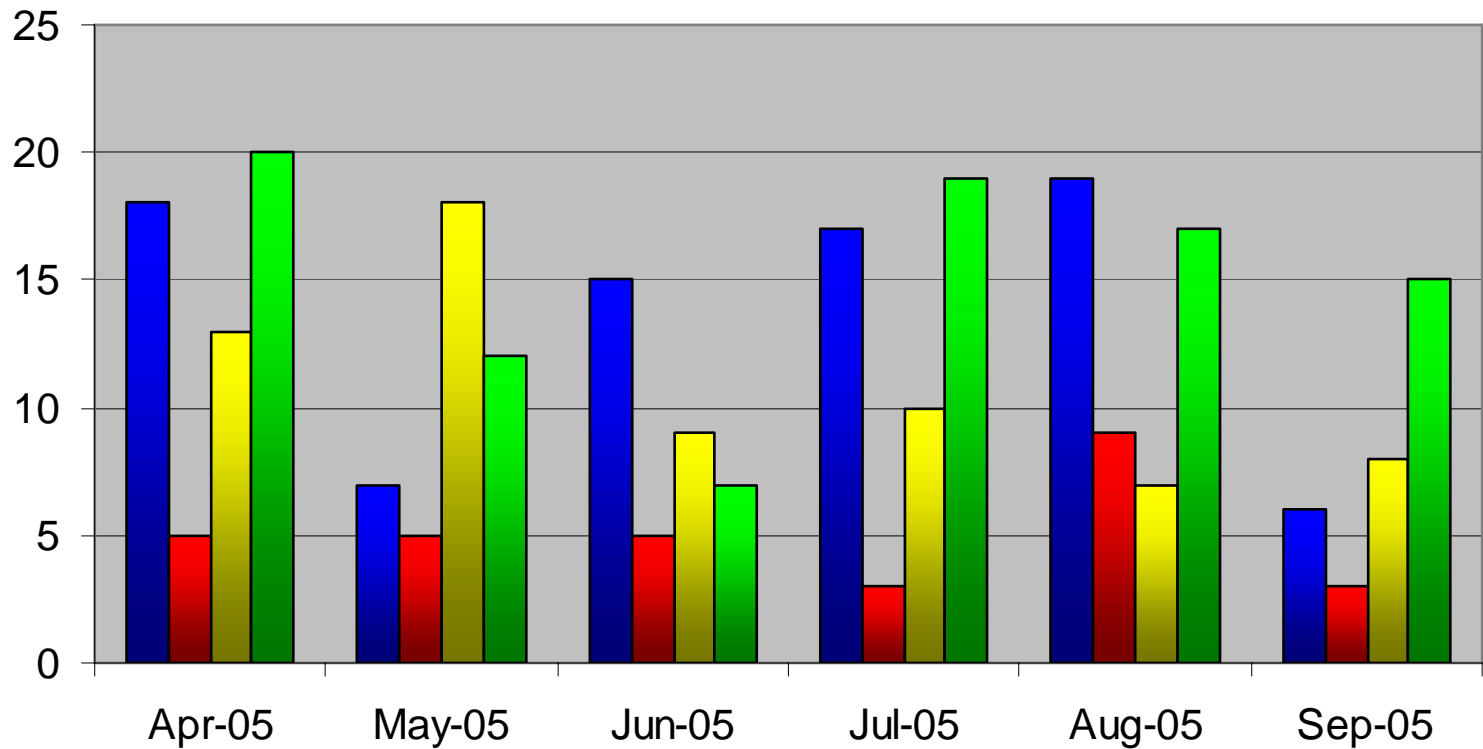


# Sample Metric



- R&D activity
- Maint & Eng activity
- Utilized for GMP activity
- Idle

# Sample Metric



	Apr-05	May-05	Jun-05	Jul-05	Aug-05	Sep-05
Com. Util.	18	7	15	17	19	6
Com. Proc.	5	5	5	3	9	3
Clin. Util.	13	18	9	10	7	8
Clin. Proc.	20	12	7	19	17	15

# Sample Metric

Metric	Target	Apr05	May05	Jun05	Jul05	Aug05	Sep05	Totals
<b>Avg. time (Man hrs) for completion of MWO (CM)</b>	2.5hrs	3.33	3.10	3.51	2.83	3.87	2.94	3.26 avg.
<b>Avg. time (Man hrs) for completion of MWO (PM)</b>	4.0hrs	2.68	5.19	7.31	4.00	2.79	3.63	4.27 avg.
<b>Number of MWO's not reviewed within 20 days.</b>	0	0	0	0	0	0	0	0
<b>Number of planned (PM) maintenance events</b>	N/A	237	163	161	188	171	167	1087