Investigations- Get it Right the Second Time!

Our experts and teams accelerate therapeutic development℠

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Introduction and my history with investigations

Definitions

A “cause” is the answer to the question, “WHY did the event occur?

- “The hurricane knocked out the power.”

A “root cause” is the answer to the question: “What is the most basic actionable reason that answers the question, “WHY did the event occur and what could we do about it?”

- “Maintenance of the back-up generator was not maintained due to the lack of a procedure.”

A “most probable root cause” is a root cause that can be shown to be significantly more probable than any other possible cause

- “The last delivery diesel fuel was mostly likely contaminated with water”

Investigation Overview

A Written Report is a requirement of the 21CFR211.192 (The Protocol)

- Most of the important points below are formed from the Protocol

Freeze the crime scene

Get QA and technical on the floor ASAP

NOE, Minor, Major, Critical

Collect all evidence relevant to the investigation

- Not just that consistent with your first opinion

Root cause analysis

- True, and actionable
- Conclusions can only be based on evidence

My History with Investigations

Operating company history- Repligen, Genzyme, Abbvie

Consulting- Windshire Group

- All major therapeutic classes, all stages of the product life-cycle, virtual companies to multi-nationals
- Consent decree
  - Focus was on investigations/CAPAs and mentoring QA “on the floor”
  - Mentored extensively by one of the top consultants in the world on compliance aspects of investigations
- Quality system improvement
- Client’s who are having a major issue and need “the A-team”

“Secret serum”

Cell culture productivity was highly variable and too many batches had low productivity

Biggest problem was compiling all the data needed

- COA’s of raw materials, data historian process data, parameters in batch records, etc.
- Data needed to get into a composite view to allow statistical analysis of process performance

“Gemba” to New Zealand and Australia

FBS quality was found to be problematical and was likely due to annual zoonotic disease

Solution and Lessons Learned

Steps can be taken to control raw material variability

- Pooling
- Screening
- Select suppliers who protect product quality

Easy access to data is invaluable

Data and analysis was very “noisy”

- For every hypothesis there was an exception

“We’re out’a here!”

- Product was abandoned by license holder with no notice
  - Requirement was seven months
- Client was senior secured investor
  - “Get back on the market ASAP!!”
- Ongoing technical issue
  - Hot melt formulation for an oral dosage
  - White “flakes” were seen in the formulation step
- “We’re outa here!”
- World’s “smallest pharmaceutical company”
- Product was relationship-based product
  - Solved critical technical problem, re-validated, re-furbished relationship with the CMO, re-branded and…
    - “0-60 mph” in 3.0 months with re-launch
- “How did they do that?!”
  - Not aware of any subsequent related quality issues

Solution and Lessons Learned

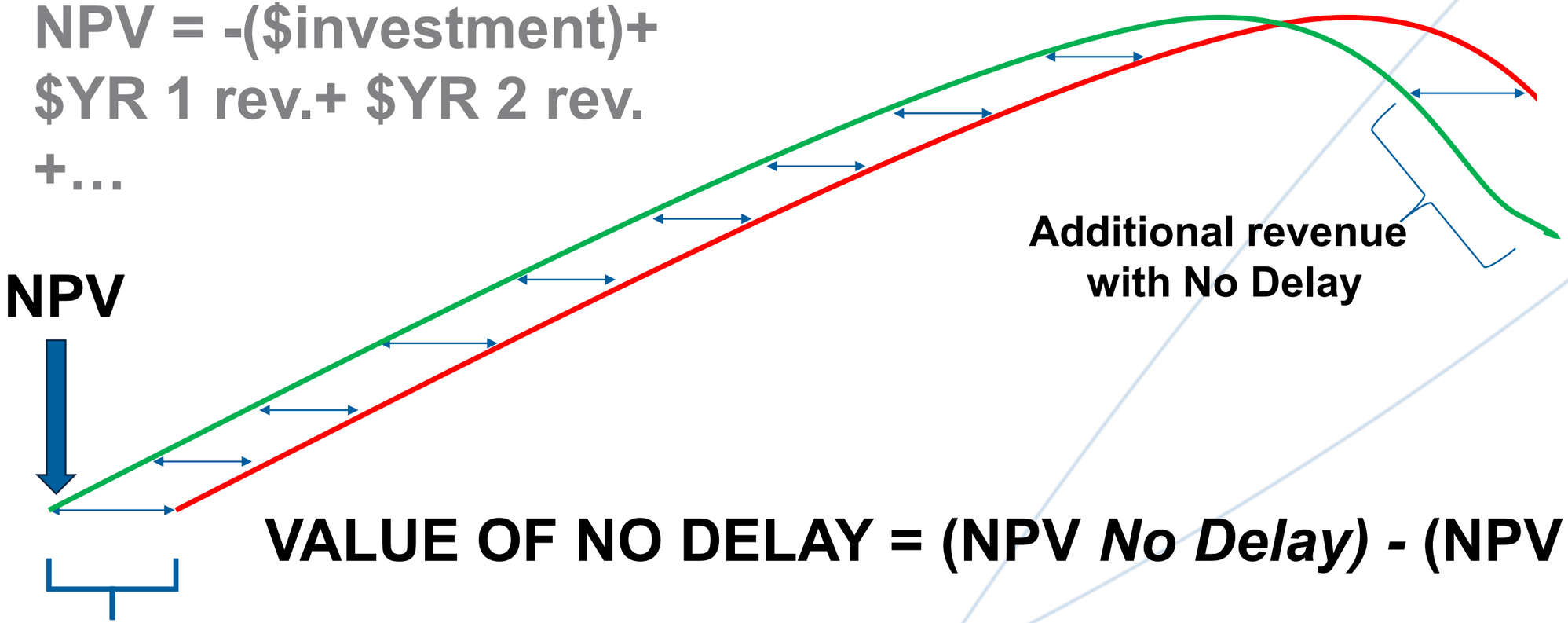
- Order of mixing of excipients with the API and melt step time was key to solving problem
- Analytics were key to establishing to risk to patient and white flakes were product related impurities
- Technical expertise and problem-solving ability was critical

“Biggest investigation of all time”

- Adventitious agent contamination
- Subject of a previous Consent Decree
- History of contamination prior to PAI
- High potential to delay approval
- Root cause and CAPA
- Day 4 of 5 of PAI
  - “I never want to hear THAT WORD in this facility EVER AGAIN!!”
  - Knew I had won!
- One year delay in approval was very plausible
  - Additional investigation, additional runs to show process was in control (not “three and out”); analyze and compile data, write report, “dance” with FDA
- How important was this investigation?

NPV Scenario for *No Delay* Versus *Delay*

NPV = -($investment)+
$YR 1 rev.+ $YR 2 rev.
+…



VALUE OF NO DELAY = (NPV *No Delay)* - (NPV *Delay)*

For One Year Delay What Would Have Been the Impact?

NPV > $8.5B!

THAT WORD WAS NEVER HEARD IN THAT FACILITY AGAIN!!

No delay greatly improved quality of life for many patients and since some indications are life threatening hopefully lives were saved!

Solution and Lessons Learned

- New treatment of feed solution for cell culture bioreactor and implementation of a new sterilizing 0.1 micron filter
  - Not all filters of the same nominal pore size are created equal
    - Pore size (i.e., physical sieving) is not the dominant filtration mechanism
      - Electrostatic adsorption
- Raw materials and operators can be sources of adventitious agents for media prep
- “First principles” led to rationalization of root cause

“The flu, who knew”

- Multi-national corporation
  - Major supplier of flu vaccine
  - Production was way down and highly variable
  - Viral propagation, egg-based process
- “James we need the A-team!”
- Gemba
  - Pointed at the practice for a step being used for viral propagation
    - “No, No, No, you shouldn’t being doing it that way!”

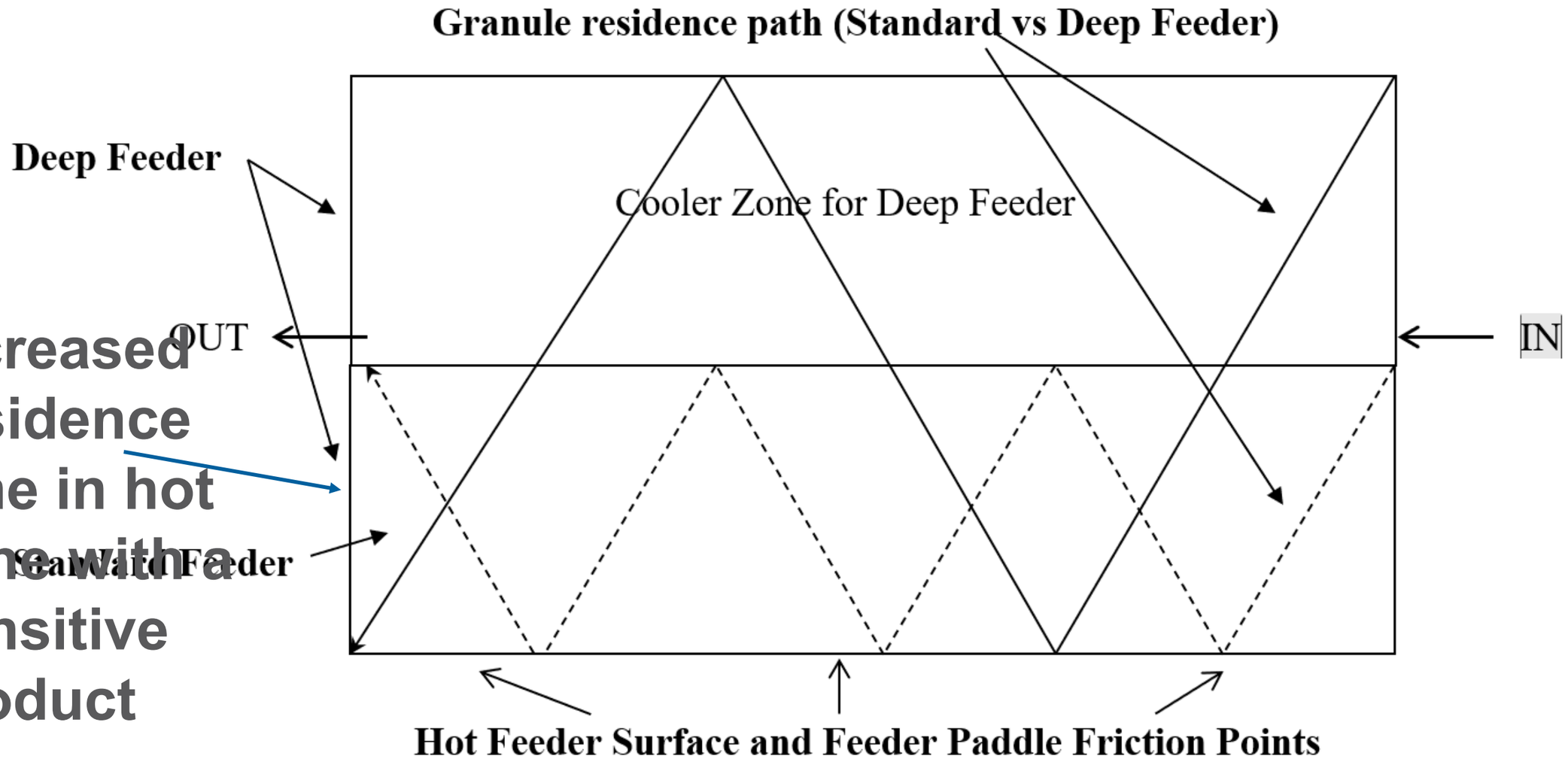
Solution and Lessons Learned

- Ensured more robustness around viral propagation step
- Gemba with expert (“another set of eyes”) was key

“Flash in a Pan”

- Oral dosage tablets were getting charring
- A number of potential root causes existed- Ishikawa
- The investigation revealed a change to the feeder for the compression machine
- CMO maintained that feeder could not be the issue
  - “It’s never been a problem before!”
- A thought experiment was used to model product in the feeder could be the root cause

Tableting speed didn't change
Rate of granules in and out were same in both feeder scenarios



Increased residence time in hot zone with a sensitive product

Solution and Lessons Learned

- Changed the feeder back to the original feeder
- “Easy” application of first principles solved the problem without extensive experimentation and the associated delay proposed by the CDMO
- CMOs need significant oversight on important investigations
  - Human resources needed to do a proper job are expensive

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Most common mistakes

Common Mistakes- Parts of an Investigation

- **Introduction and Background**
  - Assuming that the reviewer will know what the writer or investigator knows
  - Inadequate description of the product, the stage, the process, the equipment, etc.
  - No description of what is the normal function/purpose of the (what every is involved, e.g., equipment
  - No description of any requirements, e.g. acceptance criteria/specifications
- **Description of Event**
  - Including the Why
    - Goes in **Root Cause** section
  - Including hearsay or opinions

- Inaccurate description can send investigation in wrong direction
  - Need WHAT?, WHEN?, WHERE?, WHO?, HOW MUCH?/ HOW MANY?
- Not including all the known batches or product involved (more on this later)
- Not including how the event was discovered
- No clear description of the exact nature of the deviation
- Including dissimilar events in same investigation

Immediate Actions

- No or inadequate description of actions taken in response, including samples, documents, etc. impounded to aid investigation
  - Describe how the impact of the specific was prevented or limited before the investigation was initiated

- **Investigation Plan**
  - Initial impact assessment jumps to conclusions about root cause unless root cause was obvious or already known
  - Misclassification of Minor, Major, Critical
    - Common problem at CMOs
    - Not basing classification on **POTENTIAL** risk (unless root cause is already known)
  - No clear direction on how: the investigation approach; how it will proceed, resources
- **Description of Investigation**
  - Little or poor description of investigation activities, their thoroughness and facts and findings
  - Not describing sources of information, e.g. interviews, documents, etc.
  - Document everything!
  - Not scanning documents and photos to preserve them

- **Analysis of Facts and Findings**
  - Not using a root cause analysis tool most appropriate for the investigation
    - Five Whys often sufficient for simple events
    - IS/IS NOT (Kepner Tregoe) is my favorite for complex and challenging events
  - Not using combinations of root cause tools, e.g.
    - Ishikawa followed by Five Whys
    - Is/Is Not (Kepner Tregoe) followed by Five Whys
  - Not creating a list of all reasonable causes of the event
    - Method of elimination
  - Not using well controlled studies/tests when needed
  - Collecting information and calling it a root cause analysis
  - Not continuing until the (most probable) root cause is found
- **Impact Analysis**
  - Not using the entire body of information, e.g. root cause, investigation facts, scientific literature or rationale

- Not considering all the types of impacts that may have occurred
- Not describing how such impacts could be detected
- Not assessing impact to SISPQ
- Not reassessing initial impact assessment

- **Conclusions**
  - Not basing them on the previous investigation and analysis
  - Having inconsistent conclusions
  - Not assuring conclusions are understandable by all the audiences
  - Not ensuring conclusions are usable for defining CAPAs and other actions
  - Not providing supporting information and logic
  - Containing opinions or speculation
  - Containing event description, root cause activities
  - Unsupported statements about root cause or impact
  - Stating CAPAs as conclusions

- **CAPAs**
  - Not designed to correct problem(s) defined by root cause
  - Not adequate to prevent recurrence
  - Not appropriate to both the degree of impact and the events estimated frequency of occurrence of root cause (if left uncorrected)
  - Not utilizing interim action and controls
  - Continuing an investigation after it has been completed, and approved, e.g.,
    - a CAPA that test results will be evaluated when they are received
    - a CAPA to review an investigation report from a CMO
  - Counting as a CAPA an improvement opportunity unrelated to root cause

- Effectiveness checks
  - Doesn’t explain how the amount of time for the Effectiveness Check is sufficient
  - Not including a statement of whether further checks will be necessary
- References and attachments
  - Not using authoritative or reliable sources

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Stage appropriate considerations

Stage Appropriate Considerations

Extent and level of investigation for early phase products is not as extensive as for commercial product

- Except where the potential to impact SISPQ is involved or for an OOS
  - Patient safety is paramount

For Phase 1 clinical studies, unexpected or quality events can be appended to batch record if patient safety is not impacted

- That assessment requires a proper investigation
  - The complexity is driven by the severity of the incident, i.e., potential to impact patient safety
  - Impact to SISPQ or patient can't be determined until root cause is determined
- A formal deviation/investigation system is recommended
  - A simple one is usually isn't hard to do
    - No excuse not to implement one

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Elements of a world class system

Elements of a World Class System

- Design system to focus investigation effort and resources proportionate to risk
- Allocate resources based on risk classification
- Investigation group needs to be independent and free of external influence to ensure investigations and CAPAs meet SISPQ quality and compliance requirements
- Have highly trained and skilled investigators for more important investigations
  - Make position prestigious
  - Train on writing investigations using defined template and qualify investigators based on evaluation of writing
  - Consider making your investigation system a training ground for future leaders
- Investigations of high risk should be reviewed by highly competent, person highly versed in CMC regulatory compliance, technical, and SISPQ risk assessment s
- Track performance and KPIs to show improvement, e.g., amount of product in inventory, number of deviations per batch

Power of an Effective Investigation System! (Amgen)

95% reduction on errors per lot

$140M savings in 6 years
-fewer investigations
-fewer scrap lots
-less product held in inventory

The core principles can be used by all companies- even First asset companies outsourcing manufacturing

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CDMO considerations

CDMO Considerations

- The sponsor is ultimately responsible for all quality
  - This is the most important leverage point you have
  - Don’t sign off on anything that does not meet proper quality standards
- Thus, the most critical aspects of the CDMOs quality system needs to be subordinate to the Sponsor
  - Including investigations for Major, Critical, and OOSs
- Be careful of Majors being swept “under the rug” as Minors
- For technically challenging and Critical investigations the CDMO will often need sponsor support
- Do not be afraid to negotiate and seek terms in the quality agreement that support quality and are favorable to you and give you more veto power
  - Understand risk and know what your “must haves” are
    - E.g., right to supplement, review, and approve an OOS

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The future of investigations

The Future of Investigations

Investigations will become easier in the future

Data is becoming more integrated and accessible

- Easier to perform analysis and document sources

Engineered controls and parametric release reduce errors

Integrated systems will enable alerts from QMS as soon as an exception is recorded

- Get QA on the floor quickly
- Faster close
  - Some products need to have investigations completed very close to time of manufacture
    - E.g., autologous CGTs

Will there be a role for AI?

- Undoubtedly

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Take Homes and My Key Lessons Learned

Take Homes and My Key Lessons Learned

Get to true, actionable root cause

- “Get it right the second time!”
- Ensures effective CAPA

You don’t have to be a multi-national to have a highly effective and “world class” investigation quality system

Leverage scientific first principles- “Occam’s Razor”

CMO business model frequently doesn’t support adequate investigations

- Sponsors often need to supplement CMO investigations

Both incompetent and highly skilled people are expensive

- But incompetent people are more expensive
- Incompetence is usually the result of improper training and not assigning people with the requisite technical skills proportionate to the risk of the deviation

Make sure high-risk investigations are assigned Major or Critical

- Be careful of Majors being swept “under the rug” as Minors, including CMOs

Get the right people on the problem whether you are a first asset company or a multi-national

- Training and effective use of root cause analysis tools is essential
- There is no substitute for technical, scientific, and regulatory compliance expertise
- Talent involved should be proportionate to the problem

Gemba- “Walk the Floor”

- Review procedures
- Talk to operators and support personnel
- Get to the crime scene while it is fresh (ASAP)

Data, data, data!

- “My problem isn’t solving the problem, it’s getting my hands on the data to solve the problem!”

Root analysis tools can help teams organize and discuss data in a rationale, objective way

- Select the right tools for the problem!

Dr. Blackwell’s Maxim of Manufacturing Investigations

- “There will be a minimum of one data point that doesn’t agree with any root cause hypothesis”
- Don’t let this throw your investigation off! Occam’s Razor

Thank You!

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