DISAPPROVED

How to recover
• Culture, how does it look?

• The consequences of cultural-behaviour are predictable, however they are usually only apparent AFTER the event has already happened

• Consequence of collective:
  • Group behaviour
  • Individual (herd behaviour)
Heinrich ratio
(fixed ratio between the 3 layers)
Reduction of fatality can be achieved by changing (your/our) behaviour

“...you knew it was going to happen sooner or later...”
There is a positive correlation between incidents and our behaviour.
CONSEQUENCES

• Reckless cycling: obvious (observable)
• Behaving in a non-aseptic manner: not very obvious

• As a result: continuously monitor your handling
• The result of “unsafe” handling is almost never immediately observable in our industry, especially not during aseptic handling.
• GMP, in other words “preventing misery”.

Can be achieved trough continuous vigilance!
And: risk avoidance!
“Effect of cultural behaviour is hard to determine for yourselves”

- Blind spot / Inadvertedly incompetent
INSPECTION FAILURE
CAUSED BY (?)

Cause

- Training/HR
- Management
- Technical issues
- disfunctioning QMS
- ..........

Training/HR

- WFI biofilm
- Autoclave disfunctioning
- No PM programme
- Old building: no correct flows
- Contaminations due to old building.....
CAUSE (?)

• If dis-approved, normally:
• Mix of factors however absence of “Quality Culture” is predominant.
• To better specify a “lack of Quality Culture”:
  – No eye for detail
  – No knowledge management
  – “taking for granted” mentality
  – Carelessness/Disinterest/Indifference
  – No eye for performance
  – ...............
• Accept the message, and move-on.
PROJECT RECOVERY
PEOPLE

- Former: incompetency, non-compliances generally excepted.
  - Training in all aspects (GMP/technical)
  - Consultancy hired for critical operations to train people.
  - Lot of people left the company
  - Still issues with competency.
  - **Strengthened** Project Team to train On The Job people to do the job rightly coming months
  - Culture of no “non-compliances” enforced.
– Former issue: BMR was not logic, very limited instructions, no Critical Process Parameters, etc
– BMR’s for processing implemented
  • Process mapped into all details
  • Instructive Batch Records for each single step including CPP etc.
  • Risk based approach to CPP (Critical Process Parameter) and CQA (Critical Quality Attribute)
PROCESSING

- Former issue: Process Validation, just run 3 batches.
- FDA (and ICH-Q8/10) Process Validation approach

• Couldn’t do in full, since file built-up (design phase) hasn’t been done in earlier years (FDA guidance: 2008/2011)
• Solved by collecting historical data and files provided by the inventers of process
• Full Process Validation planned, first conclusions after 3 batches, will continue (reduced most probably) until Column Life Time study is finished. Post this activity: Continuous Verification.
• Manufacturing process detailed, PFD’s developed
– Former issue: Cleaning Validation scattered, no risk based approach, not in full, WCL/WCS not identified.

– FDA (and ICH-Q8/10) Process Validation approach
  • Principles has been written.
  • During Process Validation, a lot of samples will be taken based on assessment of SME’s, for Cleaning Validation.
  • Might be that some tests might be repeated due to findings by implementing the Principles in full
• Former issue: Aseptic Processing not adequate (too many open handlings)
  – Biggest issues: solutions known
  – FMEA on Sterility Assurance Level planned in (coached by experienced consultant), to detect smaller issues
  – Change Control to be written, expecting to change the way we manufacture (no process change)
Former issue: multiple systems (multiple sites), systems check: everything in place, nothing worked.

Green Field approach

- Issues with some SME’s leaving the company, readiness date shifted.
- 5 critical systems: issues with “quality” of inputs and follow-up (DSP). Up to date, repair and impact assessments (done by Project-team)
- Post implementation; full checks by Consultants/Project-team, to get complete files and training on the job.
QMS

- Operating Guidelines
- Delay in writing and implementing, Strengthened Project Team to increase speed. Expecting to be ready (for the QMS-processes) date X, with authorization and gaps filled, date Y with full implementation.
- PV, CLV still ongoing (work in process)
- Global Guidelines need updates (still) while implementation is ongoing, and needs full project attention (still).
- Some Global Guidelines not written due to change in insights, e.g. for Validation Master Plans
QMS

• Former Issues: no system in place to do check on performance, Senior Management not involved in Quality Performance.
  – MQR, since date X onwards done Monthly Management Review, based on Quality Performance Reports (MQR)
  – Z-times Global Quarterly done, first to get feeling for the system, second was actually looking into more details.
  – System is becoming more mature, but need 2 months more to get really familiarized with it.
  – More details of the problems need to be added.
  – Recently started with metrics/KPI’s, need “calibration” during coming 2 months.
• Former Issue: SOP’s not much details, wrong order different place, different approach
  – Almost all SOP’s rewritten to get it in the right order
  – Secondly to have more details
  – Another advantage: training of people
  – Now for QMS critical systems: full harmonization is taking place.
  – Continuous effort to train people on SOP’s helped by external consultants
  – Not at the required level, however significant progress observed
  – Coming months the project team will continue to oversee that training of workforce on SOP’s will be performed.
EQUIPMENT AND FACILITIES

Former: arguing into compliance, no attention for details.

- New Global Guidelines, files were missing: repair still ongoing but minority
- Content of Equipment Qualification (EQ) Files: issues
- Hiring consultancy to look into the details, together with team available for this task.
- New EQ’s to get full attention.
Former: Autoclaves, with wrong thermal indicators, no real focus on air removal, sensors at the wrong position, etc.

(Other project: no TC’s but miniature Pt-100’s)

- Hired external expert, formed internal expert team.
- Lot of issues by getting autoclaves working according international standards, delay was there, finishing is expected
- Same with Clean Steam and Pharmaceutical Water Systems.
**RISK MANAGEMENT**

- Former: very limited attention to Quality Risk Management
  - Started with Risk Ranking approach and Mind Mapping.
  - Supply Chain Mind mapped, but not yet QA-ed.
  - FMEA’s done fragmented, but not yet strategically chosen.
  - As a result: recently installed 2 Risk Managers.
  - Coming Month: Risk Management Master Plan (a Global Guideline) to be issued with overall strategy.
• Review work (effectivity check) behind schedule and Project team needed to be strengthened due
<table>
<thead>
<tr>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile filtration</td>
<td>OOS/OOT</td>
<td>Sterility testing</td>
</tr>
<tr>
<td>Analytical Method Validation</td>
<td>Reference Materials</td>
<td>Complaint handling</td>
</tr>
<tr>
<td>Cleanroom Behaviour</td>
<td>Transportation</td>
<td>Product recall</td>
</tr>
<tr>
<td>Validation of Steam Sterilizer</td>
<td>Water and Steam Systems</td>
<td>Risk management</td>
</tr>
<tr>
<td>Calibration Guidance</td>
<td></td>
<td>Sampling</td>
</tr>
<tr>
<td>CAPA</td>
<td>Technology Transfer</td>
<td>Process validation</td>
</tr>
<tr>
<td>Change Management</td>
<td>Printed Packaging/ Artwork/ Labeling</td>
<td>Clean room design</td>
</tr>
<tr>
<td>Deviation Handling</td>
<td>Media Fill Validation</td>
<td>Annual product review</td>
</tr>
<tr>
<td>Cleaning Validation - Pharma</td>
<td>Maintenance</td>
<td>Validation master plan</td>
</tr>
<tr>
<td>Cleaning Validation - Vaccines</td>
<td>Clean Construction Management</td>
<td>Investigation</td>
</tr>
<tr>
<td>Computerized System Validation</td>
<td></td>
<td>Stability studies</td>
</tr>
<tr>
<td>Disinfectant Effectiveness</td>
<td>Facility Shutdown &amp; Restart</td>
<td>Documentation and data control</td>
</tr>
<tr>
<td>Environment Monitoring Program</td>
<td>HVAC and air handling system</td>
<td>Ground rules</td>
</tr>
<tr>
<td>Equipment Qualification</td>
<td>Pest Control</td>
<td>Batch Records</td>
</tr>
<tr>
<td>Regulatory Inspection Management</td>
<td></td>
<td>Compressed gas and vacuum</td>
</tr>
<tr>
<td>Self Inspection</td>
<td>Waste Disposal Management</td>
<td>Individual department responsibilities</td>
</tr>
<tr>
<td>Shipping Validation</td>
<td>Animal House Management</td>
<td>Specification management</td>
</tr>
<tr>
<td>Training &amp; Personnel Qualification</td>
<td></td>
<td>Pharmacovigilance</td>
</tr>
<tr>
<td>Vendor Qualification</td>
<td>Status Labels</td>
<td></td>
</tr>
<tr>
<td>Warehousing</td>
<td>IPQA</td>
<td></td>
</tr>
</tbody>
</table>
8. AFSLUITING

- Relatie tussen risico op incidenten en ons gedrag

- Effect van eigen gedrag is lastig te bepalen.

- Risico mijdend gedrag (voorkom ellende) dient centraal te staan.

THANK YOU FOR YOUR ATTENTION