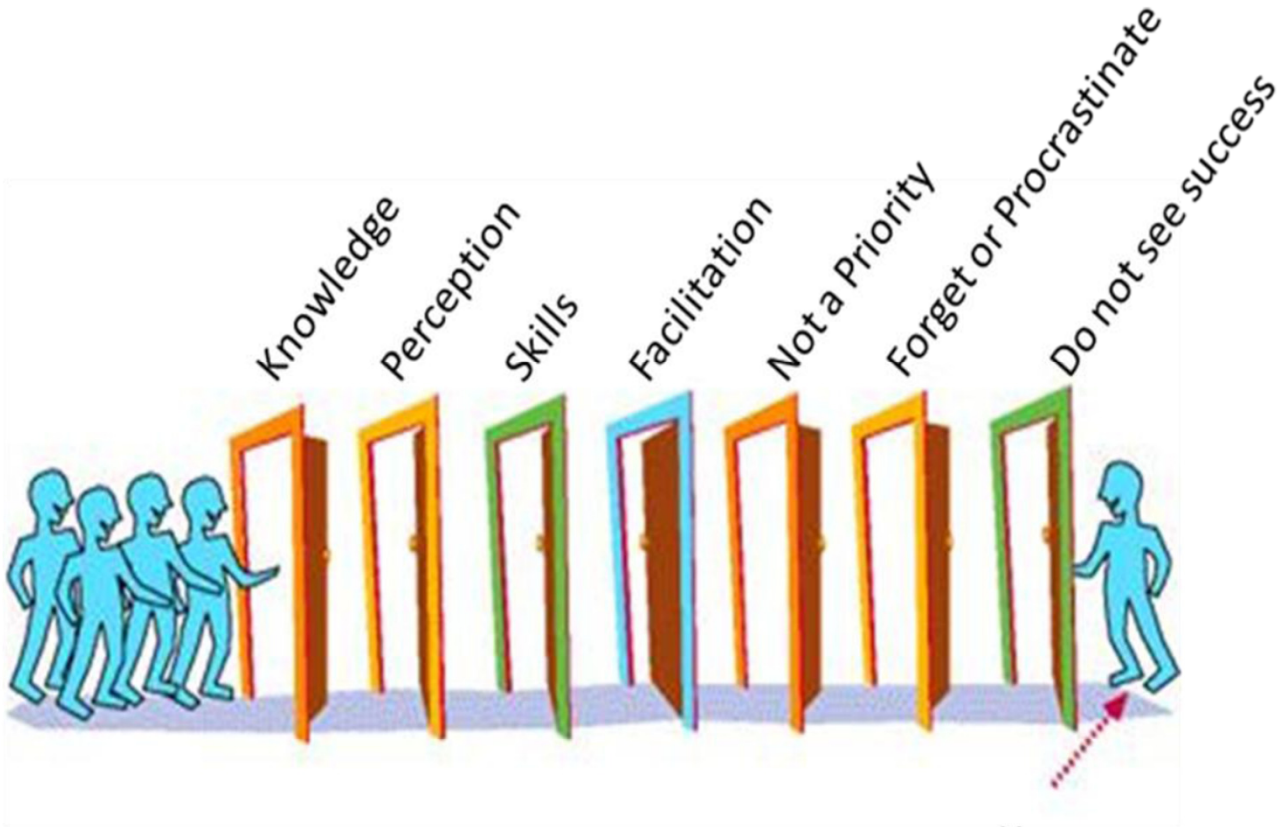
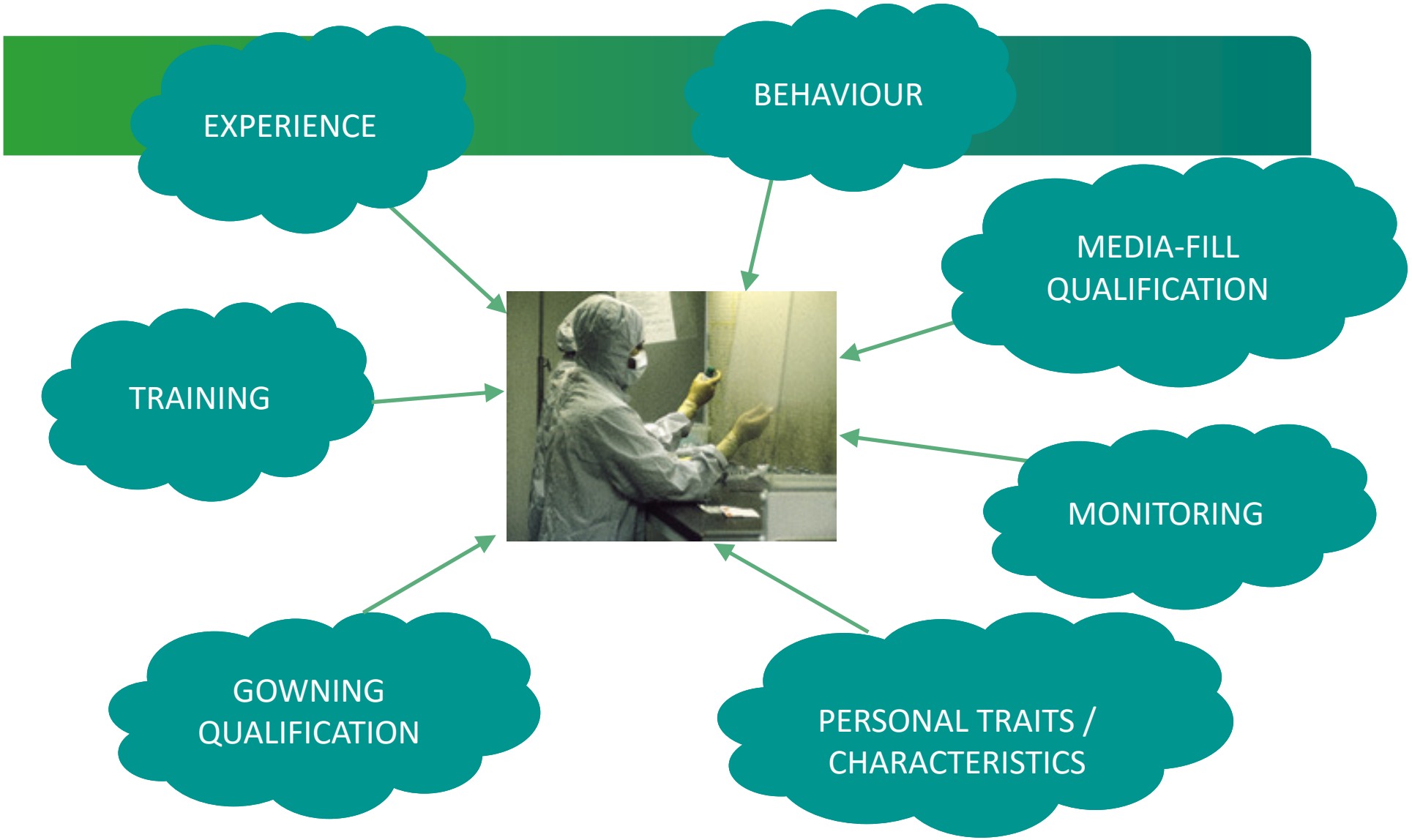

PHARMACEUTICAL
CONSULTANCY
SERVICES
DISAPPROVED
How to recover

CULTURE





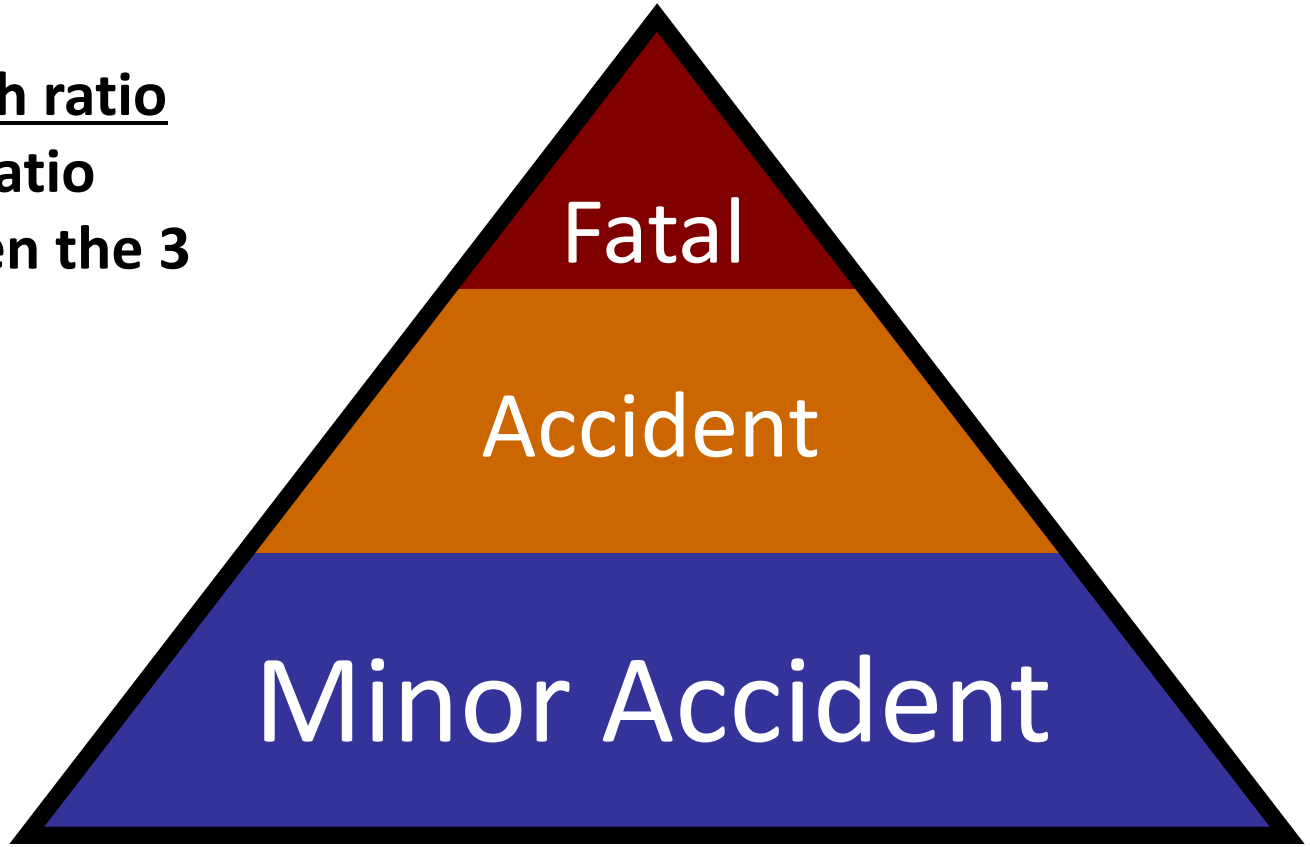
CULTURE / FAILURES

- 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)

CULTURAL BEHAVIOUR AND CONSEQUENCES

<u>Heinrich ratio</u>
(fixed ratio between the 3 layers)



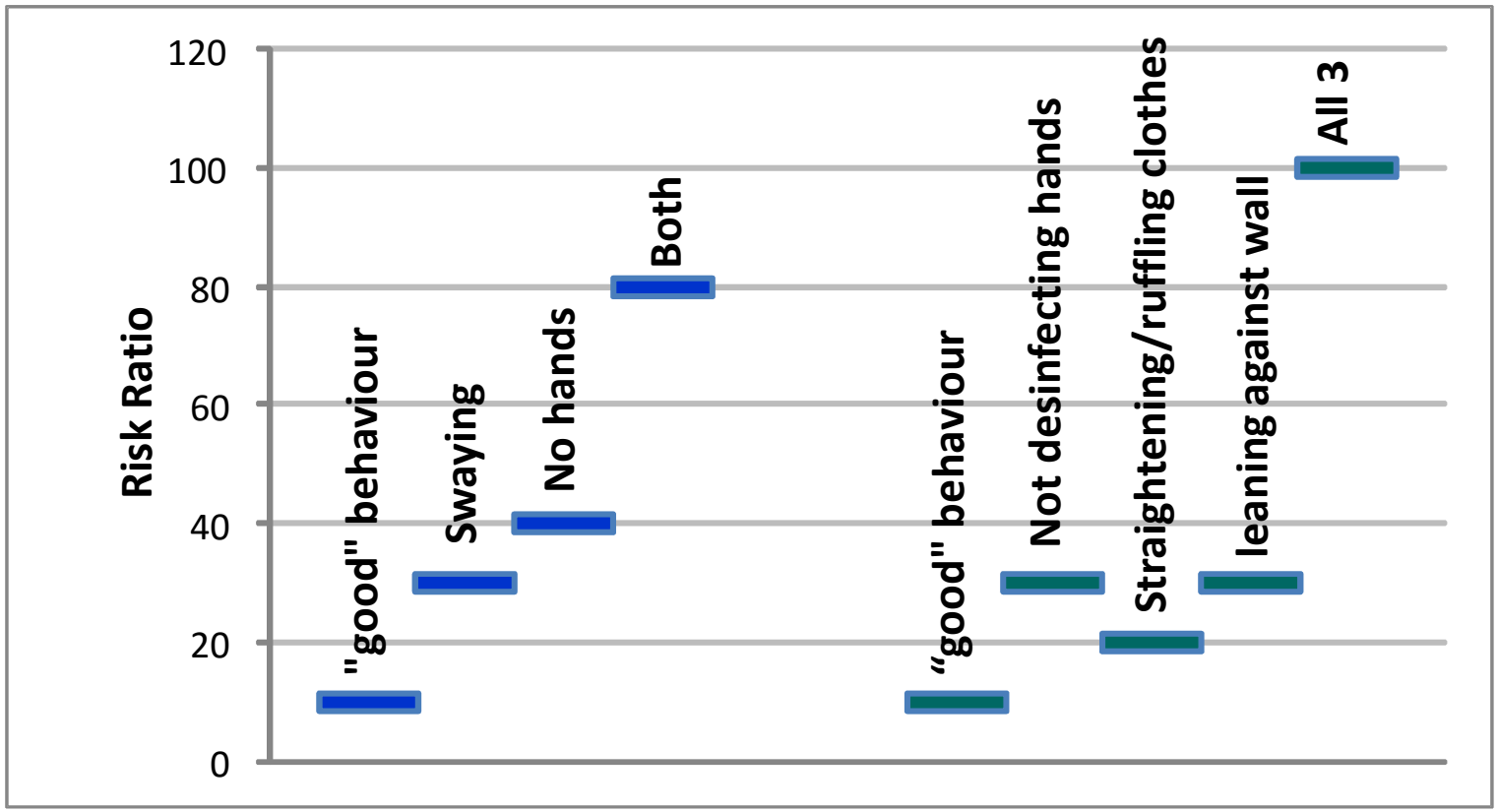
CULTURAL BEHAVIOUR AND CONSEQUENCES

Reduction of fatality can be achieved by changing (your/our) behaviour

"You knew it was going to happen sooner or later"

CULTURAL-BEHAVIOUR AND CONSEQUENCES

- 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”.

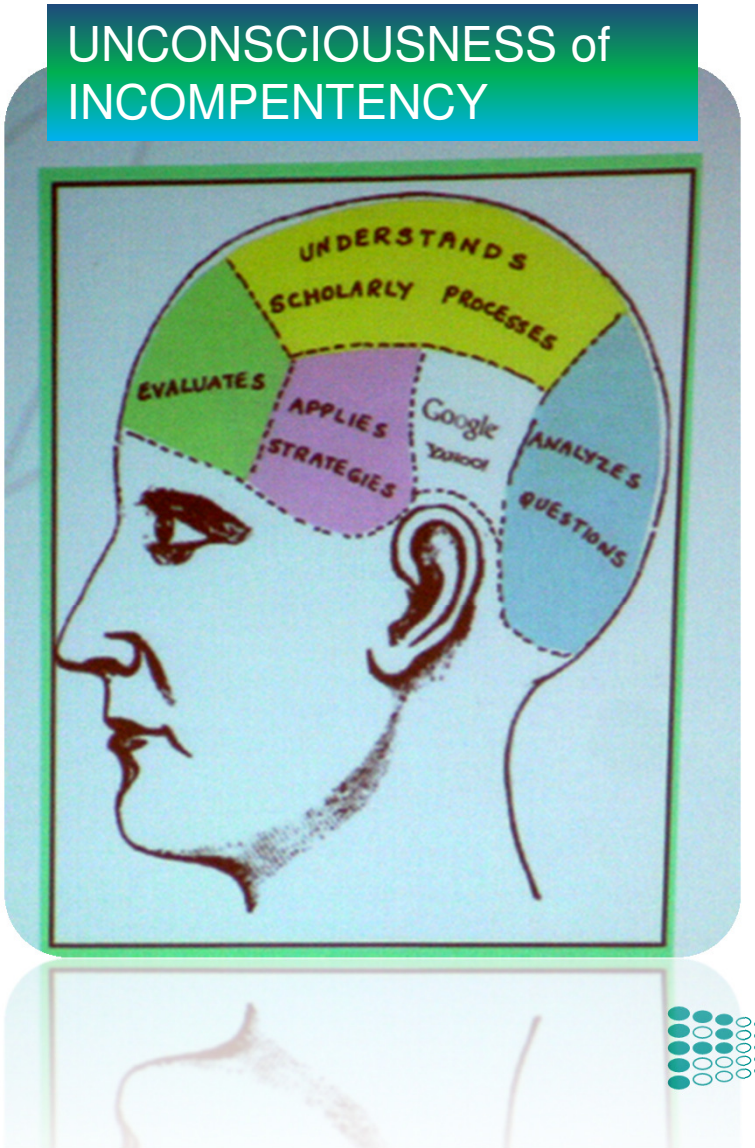
Can be achieved trough continuous vigilance !

And: risk avoidance !

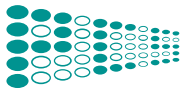
BEHAVIOUR AND CONSEQUENCES

"Effect of cultural behaviour is hard to determine for yourselves"

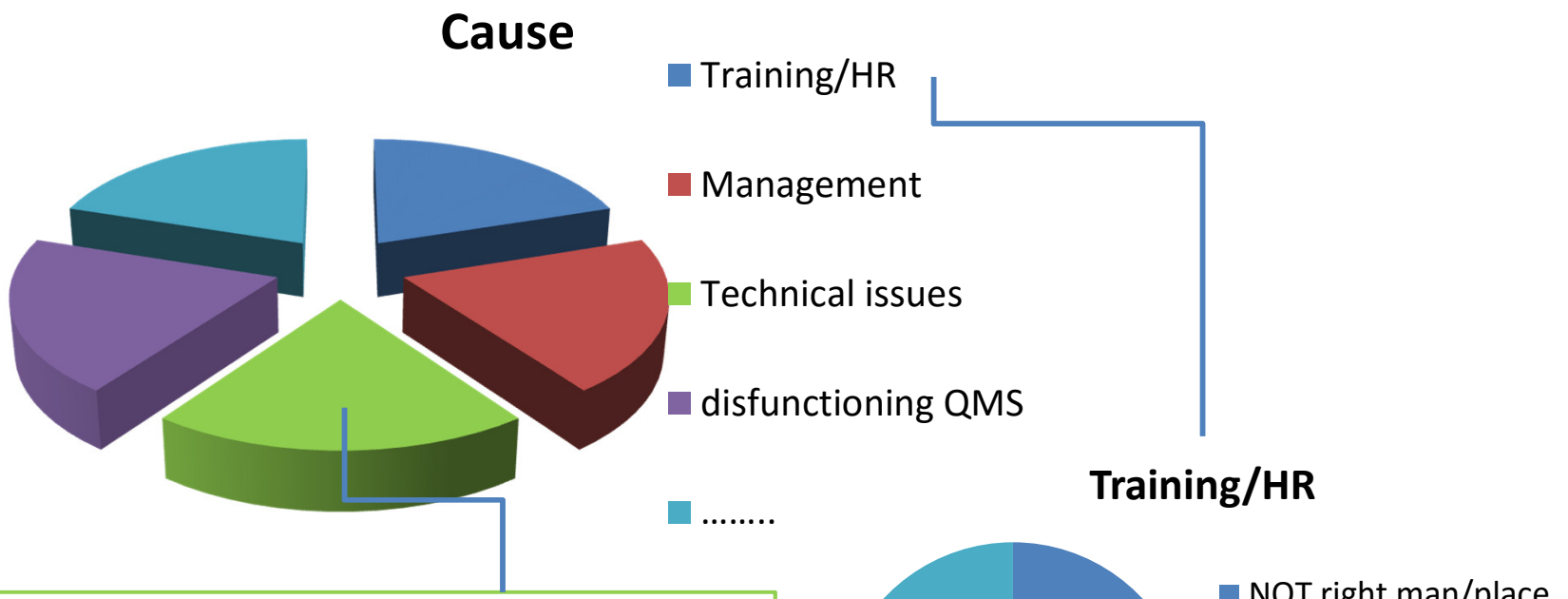
- **Blind spot / Inadvertedly incompetent**



INSPECTION FAILURE



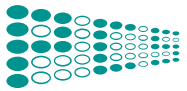
CAUSED BY (?)



- WFI biofilm
- Autoclave disfunctioning
- No PM programme
- Old building: no correct flows
- Contaminations due to old building…..

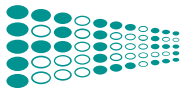
CAUSE (?)

- 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
  - ……

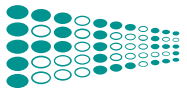


FIRST THINGS FIRST

- 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.

PROCESSING

- 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

PROCESSING

- 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

PROCESSING

- 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)

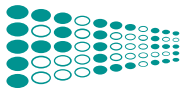
QMS

- 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.

QMS

- 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 on-going 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.

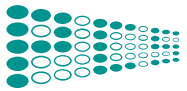
EQUIPMENT AND FACILITIES

- 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.



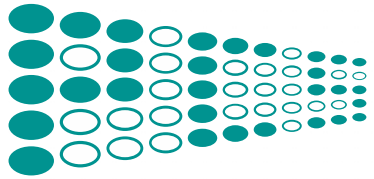
GENERAL CONCLUSION

- Review work (effectivity check) behind schedule and Project team needed to be strengthened due

GLOBAL GUIDELINES PHASES

PHASE 1	PHASE 2	PHASE 3
Sterile filtration	OOS/OOT	Sterility testing
Analytical Method Validation	Reference Materials	Complaint handling
Cleanroom Behaviour	Transportation	Product recall
Validation of Steam Sterilizer	Water and Steam Systems	Risk management
Calibration Guidance	Technology Transfer	Sampling
CAPA	Printed Packaging/ Artwork/ Labeling	Process validation
Change Management	Media Fill Validation	Clean room design
Deviation Handling	Maintenance	Annual product review
Cleaning Validation - Pharma	Clean Construction Management	Validation master plan
Cleaning Validation - Vaccines	Facility Shutdown & Restart	Investigation
Computerized System Validation	HVAC and air handling system	Stability studies
Disinfectant Effectiveness	Pest Control	Documentation and data control
Environment Monitoring Program	Waste Disposal Management	Ground rules
Equipment Qualification	Animal House Management	Batch Records
Regulatory Inspection Management	Status Labels	Compressed gas and vacuum
Self Inspection	IPQA	Individual department responsibilities
Shipping Validation		Specification management
Training & Personnel Qualification		Pharmacovigilance
Vendor Qualification		
Warehousing		

THANK YOU FOR YOUR ATTENTION



PHARMACEUTICAL
CONSULTANCY
SERVICES

Veluwemeer 112
3446 JD Woerden
T +31 (0)182 – 503 280
M +31 (0)6 – 23 047 982
F +31 (0) 182 – 502 589
info@pcs-nl.com
www.pcs-nl.com