Quality Oversight

Part I

From Compliance Check to Quality Oversight

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Dr. Georg Sindelar – my background

- Biotechnologist, started as Process Engineer fermenting MAb
- Introduction of Disposable Fermenter and of High Titre Perfusion in GMP production
- For 8 years a Pharma Compliance Consultant
- Interpreting and Consulting on new and special fields in GMP Regulations and efficient QM-Systems

chemgineering

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What is Quality-Oversight?

- Potentially not well defined – different understanding by point of view:

→ Oversight of Compliance Department over 3rd party Manufacturers?

compare WL & Guidance on Q-agreements

→ Control by physical attendance of QA staff during Operations, especially Aseptic?

„micro-Oversight“

→ Knowledge and Oversight of Management through the ranks / corporate structures over status of product quality and Quality Systems?

„Macro-Oversight“

Why do we need Quality-Oversight? Is it new?

- **Mergers** of recent decade have **blown up structures** and **hierarchies** in large global corporations **without Q-systems alignment** & direction
- Globalisation has added a cultural and language parameter to the topic
- For patients & authorities **quality awareness might have increased**
- Commercial pressure and (business) efficiency thinking might have generated the **wrong incentives** on various **management** levels

  → Warning Letters!

→ Not new but more complex: **"Quality" becomes "Quality Oversight"** with shifting demands & responsibilities

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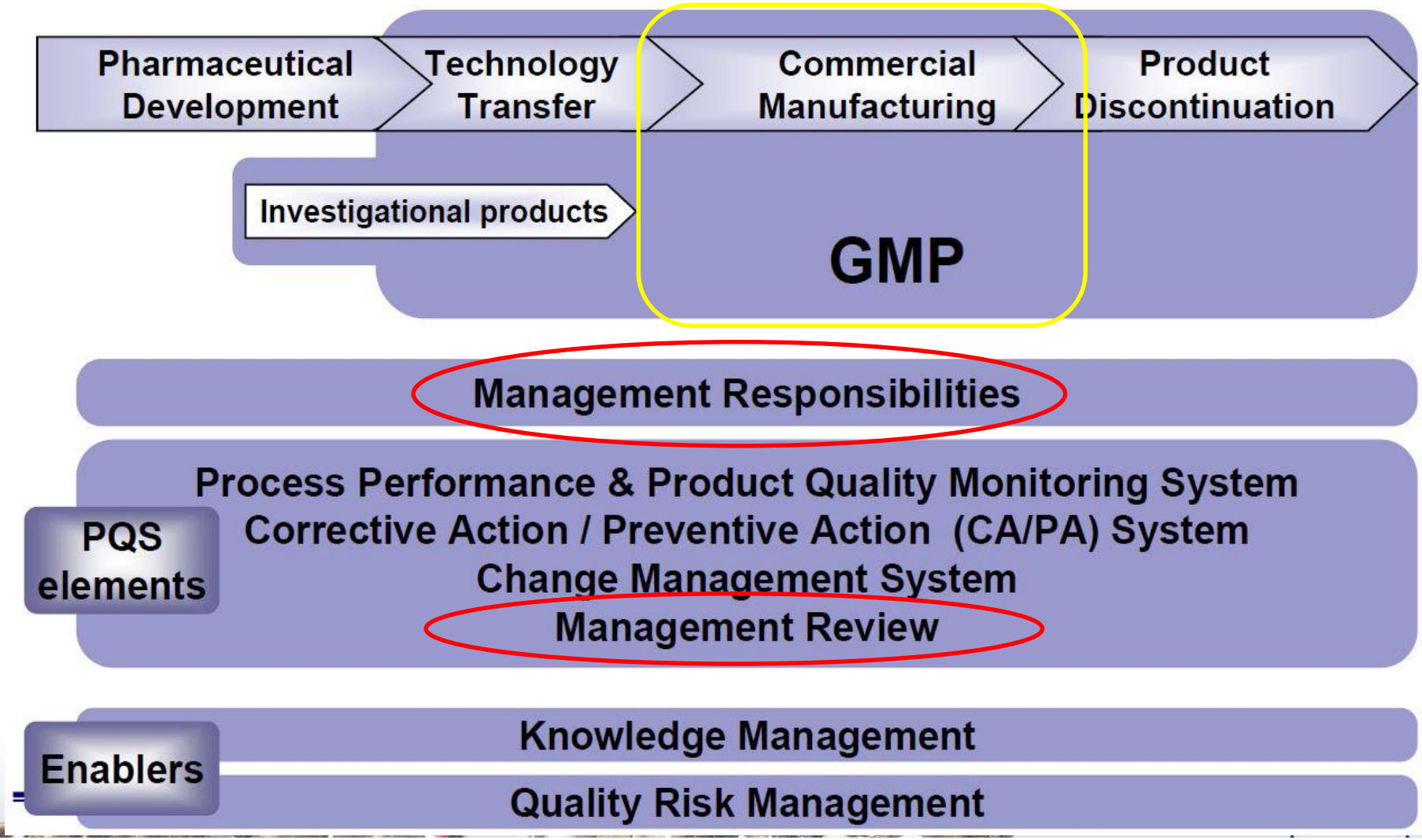
Quality *vs.* Quality-Oversight

www.ich.org



Ch1.1: „Quality Management therefore incorporates Good Manufacturing Practice“

So do we really need Quality-Oversight?

- Realization by authorities: “A fish rots from the head down”

→ New regulations installed [EU GMP p.I Chapter 1 / ICH Q10]

- Realization by (corporate) Managers: poor oversight = poor quality = high remediation costs and poor reputation
- → Tools and Systems requested

“Become an anticipating organization rather than a reactive one”

John E. Snyder, The QA Pharm: Five Obstacles to Management Oversight of the Pharmaceutical Quality System; 2013

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What does it actually mean? – Chapter 1

1.3 The size and complexity of the company's activities should be taken into consideration when developing a new **Pharmaceutical Quality System** or modifying an existing one. While some aspects of the system can be company-wide and others site-specific, the effectiveness of the system is normally demonstrated at the **site level**.

1.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System.
1.6 There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.

Means to achieve Quality-Oversight – ICH Q10

Content: §2 – Management Responsibility

„soft skills“:
- Management Commitment
- Resource Management
- Internal Communication

„tools“:
- Quality Policy
- Quality Planning → annual plan & monitor / report
- Management Review

“Includes data from a wide range of external and internal sources”

→ compare to ISO (e.g. 13485): input & output parameters

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Means to achieve Quality-Oversight – ICH Q10…

… more than just a hint to Management Review:

3.2.4 Management Review of Process Performance and Product Quality

Management review should provide assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review.

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Quality Oversight – How we get there – Case Study

Quebec, Canada. It is apparent that Novartis International AG (Novartis) is not implementing global and sustainable corrective actions. We remind you that you are responsible for ensuring that your firm's drug manufacturing operations comply with applicable requirements, including the CGMP regulations. FDA expects Novartis to undertake a comprehensive and global assessment of your manufacturing operations to ensure that drug products conform to FDA requirements. Finally, the Agency is concerned about the response of Novartis to this matter. Corporate management has the responsibility to ensure the quality, safety, and integrity of its products. Neither upper management at Novartis nor at Sandoz Inc., nor at Sandoz Canada Inc., ensured global, adequate, or timely resolution of the issues at these sites.

to be contaminated with foreign particles. Your investigation found that 22 of the 29 foreign particle types identified were **(b)(4)**. Nonetheless, your firm decided to still use these contaminated lots to produce your **(b)(4)** Capsules **(b)(4)** µg finished product. We are concerned that it was not until July 2012 that your firm began a formal project to implement comprehensive corrections to mitigate the presence of foreign particles in your **(b)(4)** API.

Why do

global (and small) Pharmaceutical Companies

lack

Quality Oversight

[and thus potentially product quality] ?

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Typical Problems & Examples
Site level – Quality Oversight starts with Quality

Complex Q-Unit structures:

- „Product-QA“ + „System-QA“ + „Operations Compliance“ (non-Q-Unit) led to poor Q-event handling / quality.
- „Systems-QA“ was involved in daily business
- Customer wanted to add another Q-Compliance ☹

Poor Responsibilities & Awareness – wrong motivation / KPIs:

- Deviation owner responsible for complete process but not empowered (work-floor operator)
- Solving Deviations not seen as high priority – „output“
  → Poor reporting of Q-events, wrong assessments, wrong Root Cause
  → Poor Overview: no common Root Causes detectable
  no Recurrence detectable

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Typical Problems
Site level – wrong responsibilities and hierarchies

- Head of QC was also Head of QM with QA department as reports → conflicting roles
- Head of QC was reviewing and signing/ authorizing daily QC activities despite some 2 extra hierarchical levels (→ wrong tasks, inefficiencies, no time left for oversight and strategic planning tasks)

- Heads of Q departments assessed internally (360° feedback) and externally as not (managerially) fit for the job

- Reluctance of corporate QM-responsible to accept site Head of QM as report ("too many reports") ☹ , thus…
- QA was planned to be made reporting to Technical Operations (Production basically) ☹

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Typical Problems – site / corporate level

Inadequate (electronic) **Tools** or Training:
- e.g. Trackwise often abused as „dump“
- Insufficient information and assessments (too tiny reporting fields)
- Poor set-up regarding searchabilty & analysis
- diverse „categories“, Q-events are not found, not consolidated
- no (formalized) Management (Q-)Review (SOP, agenda, report)
- Inefficient meetings & reporting, missing Q-boards

No awareness & evaluation of Q-situation on site level:
- wrong Root Causes (use Fishbone, 5 Why, etc.)
- no recurrence checks and definitions/categorization
- no escalation principles
- no oversight and mechanisms regarding trends: increasing open changes, deviations etc.

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Consequences of missing Quality-Oversight

What does Lack of Oversight actually mean?

→ many recurring complaints, recurring deviations, oos, reworks, rejects

→ due to unsolved issues, ineffective CAPAs, non-identified RC, (lack of (process) knowledge)

→ due to poor training & awareness, wrong motivation/ incentives / frustration, poor communication & responsibilities, time & resource restrictions

Not regularly challenged / inspected / audited

→ lack of interest and focus by management, lack of resource allocation, lack of information / input

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How to detect the problems' root cause?

→ many recurring complaints, recurring deviations, oos, reworks, rejects

→ due to unsolved issues, ineffective CAPAs, non-identified RC, (lack of (process) knowledge)

→ due to poor training & awareness, wrong motivation/ incentives / frustration, poor communication & responsibilities, time & resource restrictions

→ lack of interest and focus by management, lack of resource allocation, lack of information / input

Any of these levels can be affected.

Need **Analysis** first to fix the right ones and align them

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Analysis for missing Quality-Oversight

Often obvious: Inspection finding, Management realisation, staff frustration

What to look for – from **Compliance Check** to Quality Oversight:

Specific **Compliance Gap-Analysis**:

- check Q-events: Deviations, Complaints, oos, rejects
  - Recurrence of event and/or Root Causes
  - Volumes, trends, runtimes

- check SOPs: Deviations, Complaints, Change Control
  - Categorisation, Escalation, Due Dates
  - Responsibilities

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Analysis for missing Quality-Oversight

Specific Gap-Analysis (*cont'd*):

- Check tools / systems:
  - Well established and used?
  - Efficient work-flows?
  - Sound descriptions & assessments?

- Specific Analysis:
  - SOPs & Results Management Review / PQRs / Internal Audits
    - requirements and topics covered
    - compare to true status
    - consequences drawn

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Analysis for missing Quality-Oversight

Specific Gap-Analysis (*cont'd*):

- Interview operators & managers:
  - Responsibilities, empowerment, awareness – frustration?
  - Compare "doing" and status *vs.* SOPs
  - Compare judgement of management *vs.* status

- Meeting systems and structure:
  - Agenda, Minutes, Term Of Reference for reporting/status
  - Hierarchical Input – Output relation
  - "transparency" of systems, information dissemination
  - Specific: level-specific Q-monitoring meetings/systems
    → SOP? plan? agenda? Trend & recurrence recognition?

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Analysis for missing Quality-Oversight

Specific Gap-Analysis (*cont'd*):

- Resource use and efforts
  - Number of Q-staff per level
  - "one day in the life of" task analysis Q-staff

- Q-Structure Analysis:
  - Q-units per system / per BU / per plant / product-specific…
  - Ownership of Q-systems (complaints, CAPAs, etc.) / responsibilities
  - Corporate structures
    - Policies / SOPs → translation to site level
    - Internal corporate audits
    - Q-plans & reports

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Results of Gap-Analysis

- Impression of the Q-systems-structures of the company
  - descriptions, diagrams, flow-charts
- Knowledge on status of Q-systems and compliance level
- Perceptions of staff and management

→ **Gaps List** for aspects of Compliance & Q-Oversight:

- status Q-events / system / structures
- ownership & responsibilities
- meeting structures
- Q-measuring & -planning tools
- management involvement
- reporting & escalation structures

Implementation Steps from Gap-Analysis

1) Design individual solutions / **Remediations** for **Gaps**

→ many recurring complaints, recurring deviations, oos, reworks, rejects

→ due to unsolved issues, ineffective CAPAs, non-identified RC, (lack of (process) knowledge)

→ due to poor training & awareness, wrong motivation/ incentives / frustration, poor communication & responsibilities, time & resource restrictions

→ lack of interest and focus by management, lack of resource allocation, lack of information / input

2) Design structured approach to Q-Oversight system implementation using distinct “**Work Streams**”

Root Causes and their Remediation - I

(Corporate) Management Level:

- lack of interest and focus by management
  → raise awareness, show benefits: “cost of failure”

- lack of resource allocation
  → show benefits / profit - (ICH Q10 Annex1)

- lack of information / input
  → install Management Information System (MIS)
  → design escalation processes
  → improve use of and instructions on Q-events tools (*Trackwise, SAP etc*.)

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Root Causes and their Remediation - II

Management / Operations Level:

- poor communication & responsibilities
  - → Install systems: Meetings Structure, MIS, KPIs
  - → define & assign ownership
- wrong motivation/ incentives
  - → change/tune KPIs, install Q-planning
- frustration & poor responsibilities
  - → improve SOPs/processes, tools, discuss KPIs
  - → empower employees
- poor training & awareness
  - → train & coach employees
- time & resource restrictions
  - → optimize processes
  - → get more/other staff from upper management

Root Causes and their Remediation - III

Operations Level / QA-level:

- unsolved issues, ineffective CAPAs, non-identified RC

  → improve tools/systems
  → install monitoring
  → raise awareness & skills, train operators

- lack of (process) knowledge

  → increase knowledge (data-based / experimental)
  → raise expertise level (training & doing)
  → keep/manage know-how and SME
  → transfer & disseminate knowledge

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Root Causes and their Remediation - IV

Operations Level:

- many recurring complaints, recurring deviations, oos, reworks, rejects

→ improve processes (descriptions, MBRs),
→ improve systems, flows, SOPs
→ raise awareness, discipline & skills by training
→ check Root Causes and remediate

→ (Internal) Audit /self inspection findings should feed into the common CAPA system

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Implementation Steps from Gap-Analysis

2) Design structured approach to Q-Oversight system implementation using distinct “**Work Streams**”:

- Compliance
- Tools
- Awareness
- Management Q-Information System (MIS)

→ systematic approach

Implementation Steps from Gap-Analysis

Align above **Remediations** to "**Work Streams**"

- Compliance (SOPs, audits)
- Tools (information/metrics, escalation, Mngmt Review)
- Awareness (structures, responsib., meetings, visualization)
- Management Q-Information System (MIS)

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Implementation Steps from Gap-Analysis let's start

In place

SOP present

In use

SOP is distributed / available and trained

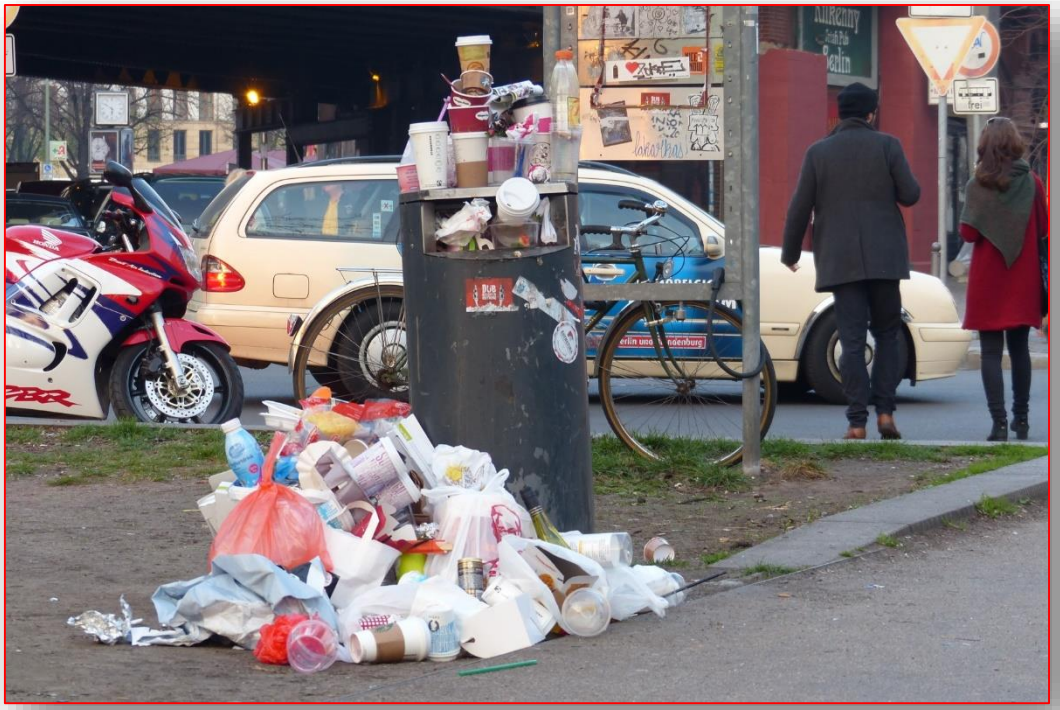
Processes follow the SOP

Under control

Employees work correctly according to SOP

Reviews show: Using the SOP-described process does not overstrain the organization

In Place - In Use - Under Control?



WS “Compliance” – SOPs, Questionnaires & Audits

How can we ensure a standardized & compliant Q-system?

- Design Compliance SOPs on corporate level
- Program to introduce and implement on site level
  - Translation to site SOPs
  - Questionnaires to individually check fulfilment of each requirement; per SOP → commitment / responsibility of site (Q-) management
    → insight into true site culture
- Corporate Audits of sites for control

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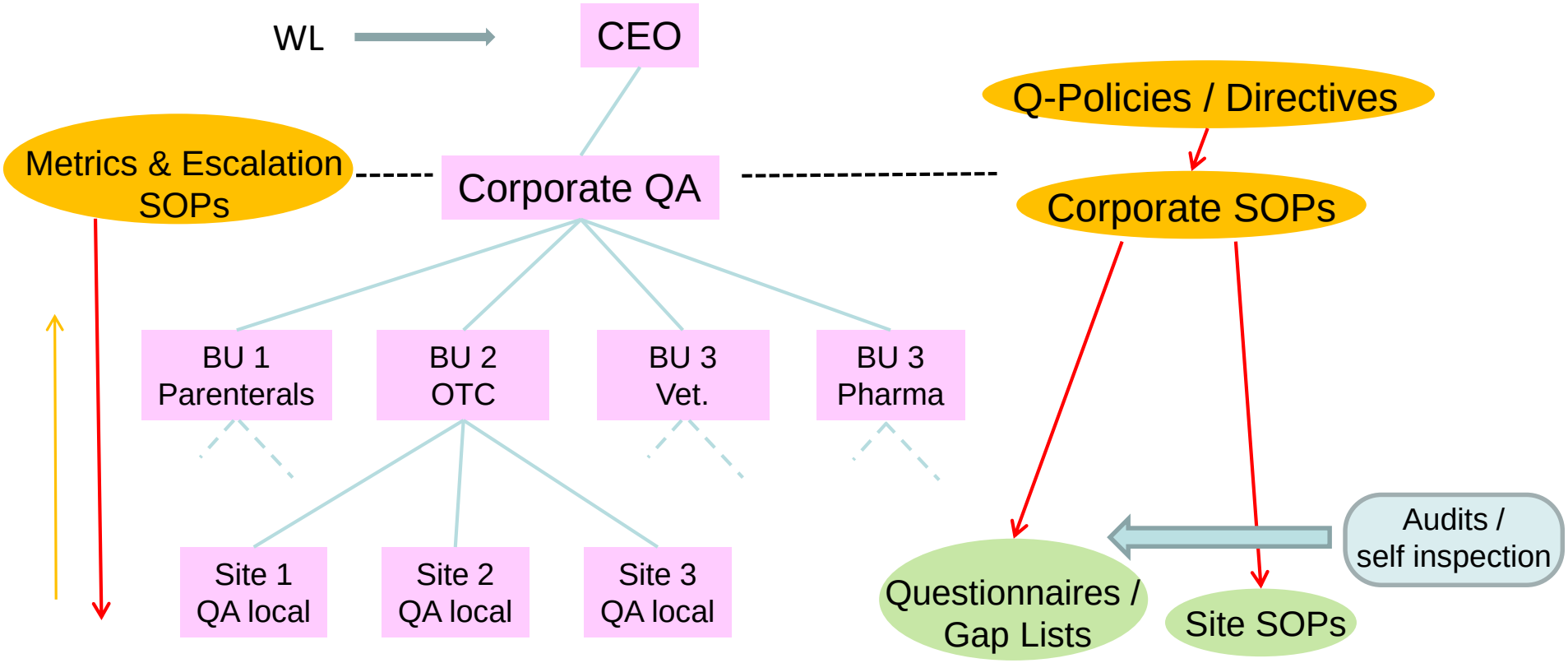
WS “Compliance” – SOPs, Questionnaires & Audits



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Work Stream “Tools” – Tool Escalation

Why escalation?

- Immediate focus and actions, high level responsibility and commitment, “global” reach
- Essential that escalation happens within a specified timeframe and is apolitical and unfettered by local approvals.
- After escalation has occurred, the **added value** is the assessment and mitigation of risk, notification to other sites, follow-up and network-wide verification, and closure.
- 21cfr part 211.180 f; ICH Q10

adapted from John E. Snyder, The QA Pharm: Five Obstacles to Management Oversight of the Pharmaceutical Quality System; 2013

Work Stream “Tools” – Tool Escalation

- Design Escalation SOP & forms/tool - link to (global) CAPA
- Categorize possible incidents and define respective actions & timelines
- Link to Monitoring results for high-risk incidents/issues/trends

Incident Category	Site Mngmnt (level 1)	Regional M. (level 2)	BU / Division (level 3)	Corporate level / CEO
critical	inform instantly	inform instantly	inform instantly	inform instantly
Major	inform (weekly)	inform (quarterly)	routine condensed KPI	No action
minor	routine condensed KPI	No action	No action	No action

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Work Stream “Tools” – Information & Metrics

What does the Organization / (Upper) Management need to know? And when?

- Status of the QM system (“does it work?”) and overall quality level:
  - → consolidated / “condensed” / aggregated parameters – few only
    - ❖ regular basis, ongoing
  - → trends – some few only, bad ones rather than good ones
    - ❖ regular basis, ongoing & if significant (-ly bad)
  - → High risk issues (potential recalls, severe adverse effects, critical product quality impacting deviations, mix-ups etc.; Warning Letters, suspensions etc.) ⇨ *risk to patient, business &/or reputation*
    - ❖ asap → “escalation” needed
  - → comparisons – diverse sites; benchmarking
    - ❖ regular basis, ongoing; on effective day

WS “Tools” – Management Review

General Approach to Metrics for Management Review;
Answer following question:

1. How well is the QM System being managed?
2. What unacceptable event or trend has the System detected?
3. What are the product quality and cGMP compliance implications and risks?
4. Where should we target specific action?

John E. Snyder, The QA Pharm: Five Obstacles to Management Oversight of the Pharmaceutical Quality System; 2013

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WS “Tools” – Management Review - Metrics

→ **What to review?** Some hints / requirements in ICH Q10 (3.2.4) *et seqq*:

(1) The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities;
(2) Periodic quality reviews, that can include:
(i) Measures of customer satisfaction such as product quality complaints and recalls;
(ii) Conclusions of process performance and product quality monitoring;
(iii)The effectiveness of process and product changes including those arising from corrective action and preventive actions.
(3) Any follow-up actions from previous management reviews *(CAPA)*.

(b) The management review system should identify appropriate actions, such as:
(1) Improvements to manufacturing processes and products;
(2) Provision, training and/or realignment of resources;
(3) Capture and dissemination of knowledge.

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WS “Tools” – Management Review - Metrics

4.1 Management Review of the Pharmaceutical Quality System

Management should have a formal process for reviewing the pharmaceutical quality system on a periodic basis. The review should include:

(a) Measurement of achievement of pharmaceutical quality system objectives;

(b) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:

(1) Complaint, deviation, CAPA and change management processes;

(2) Feedback on outsourced activities;

(3) Self-assessment processes including risk assessments, trending, and *internal* audits;

(4) External assessments such as regulatory inspections and findings and customer audits.

et seqq.

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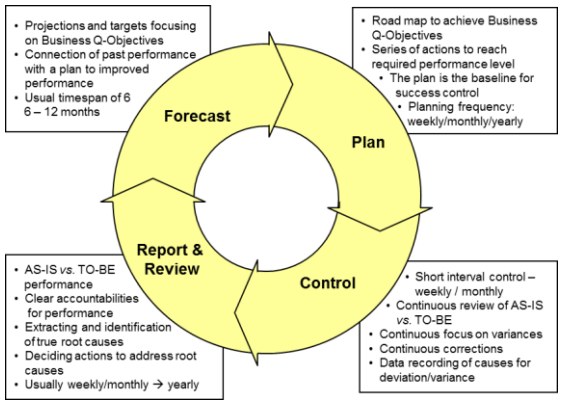
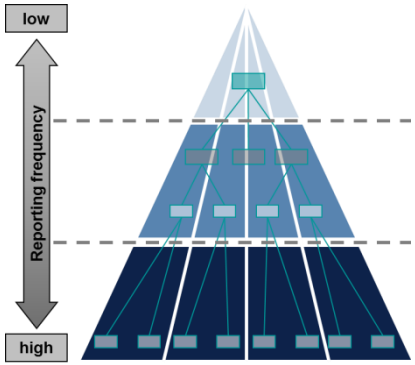
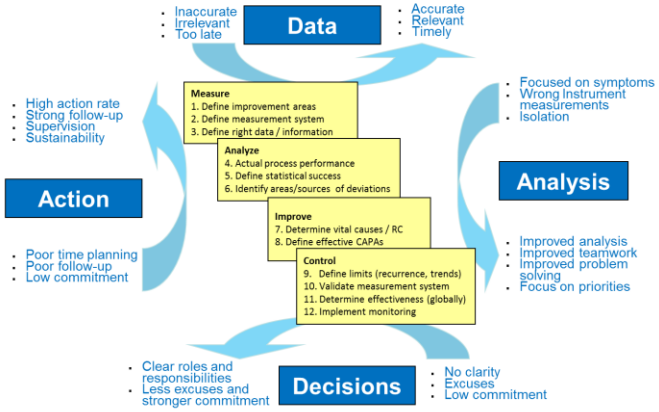
WS “Tools” – Management Review - Metrics/KPIs

…”performance indicators” →

The details of using Management Review, Metrics & “KPI”s as basis for Quality Oversight by means of a Management Information System approach will be detailed in the next part of the presentation







Work Stream “Awareness” - Meetings

Trivial but true:

- Every meeting needs a predefined agenda & report/minutes
- Agenda and Report should be standardized
  - Tool: TOR – Terms of reference & Visualization
  - Requested Input → required Output

- Finetune meetings & frequencies to match
  - Set fixed dates throughout the year
  - (more frequent at beginning)

WS “Awareness” – Meetings – TOR example

Terms of Reference for the weekly Q-Unit Status Meeting

Meeting	
Frequency	weekly
Day	every Friday
Time	09.00 - 10:00
Location	Meeting Room

	Goal
1	Q-teams exchange
2	status update & consolidation
3	risks identification
4	risks and events mitigation
5	KPI generation & feed

	Input
1	Acion Log
2	status Q-events
3	Escalation requirements?
4	further info

Participants	
Responsible	Head QA (Mr. Nice)
Required	QC Head (Ms. Pretty)
	Change coordinator (Mr Right)
Optional	Reg Aff
	Validation Team member

	Agenda		
1	Introduction	5 min	Mr. N.
2	Action Log	10 min	Mr. N.
3	Results	30 min	all
4	new Actions	15 min	all

Meeting Rules

- be punctual
- be preparaed
- no phone calls, no emailing
- timely absence notfication & backup org.
- don't interupt
- silentness means consent

	Output
1	new Action Log
2	Status Update
3	KPI Update
4	Escalation/Actions
5	improvement strategies

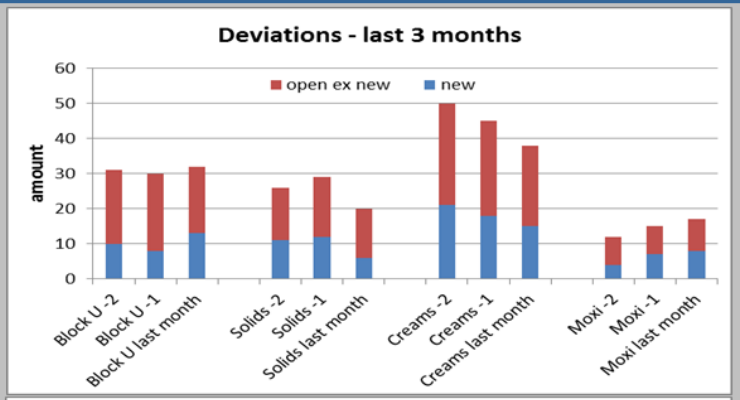
WS “Awareness” – Dashboard - visualization

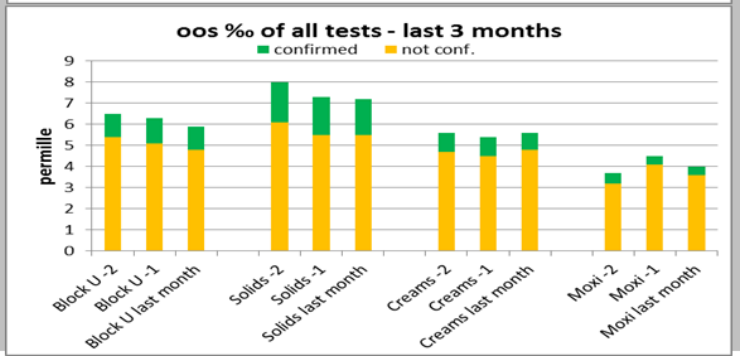
Dashboard Site Quality Board Meeting Q1 2016

Escalation Actions

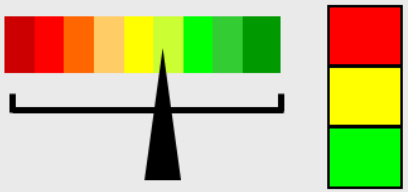
- **New: none**
- **Open: none**
- **Closed: stability failure oos#12345 solved**

Q-events comparison





Q-Plan fulfilment



– behind plan: actions?

– slight slag

– on track, no actions

29.02.2016: one item on hold, five started but delayed

Special attention: none

Quality Status – overall site

- **Major findings customer audits / inspections: none**
- **Complaints stable (new), decreasing (open)**
- **3 critical deviations**
- **Right First Time rate: 87% (decrease - last month)**

Risks, Trends, Recurrences, Dependencies

- **Open Changes increasing over whole site**
- **QC workload Micro will increase with new PW loop validation**

WS “Awareness” - Structures & Responsibilities

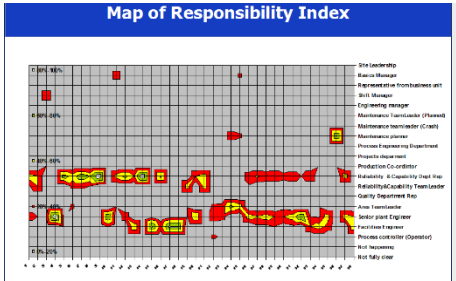
QA functions should report into corporate Q-structure (“solid *vs.* dotted line”)

- → streamline **responsibilities** & define by sound job descriptions:
  - → staff performing tasks according to organigram and SOPs as intended / designed
  - → Based on analysis: Task analysis, One-Day-in-the-Life-of, RACI tables

- → Responsibility needs **empowerment** → install **ownership**, also for KPI delivery and tracking

- → Install awareness for KPIs as quality - not as performance – measure

- → Install signature requirement systems (SOP) for management overruling of Q-unit decisions



Baseline Accomplishments

With execution & introduction of all above tasks & tools we have set the framework and prerequisites to start the **Quality Oversight Process**:

- Compliance gaps closure, improved processes & control
- Awareness (Management & Staff) & right responsibilities
- Escalation tool
- Improved meeting structures
- KPI & Metrics definition, monitoring & visualization (*next part*)
- KPI aggregation and reporting & review system (incl. Management Review) - (*next part*)

… end of Part I…

Thanks for your attention – Questions?

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