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Quality Systems

Indian Pharmaceutical Alliance

Advanced GMP Workshops 2017

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An agency of the European Union

Summary

1. Quality by Design and Product Development
2. Quality Risk Management - How have regulators and the industry adopted Quality Risk Management since 2005?
3. Current concepts of quality systems
4. Quality System Indicators and Tools to evaluate GMP compliance

1. Quality by design and product development

Quality by Design (QbD) ≠ Designing a robust Quality System

- Important to understand that QbD and the **Pharmaceutical Quality System (PQS)** **are different but complimentary**
- Art 6 of Directives 2003/94/EC and 91/412/EEC require manufacturers to establish and implement an effective **pharmaceutical quality assurance system. T**he term Pharmaceutical Quality System is used in the interests of consistency with ICH Q10 terminology
- **Pharmaceutical Quality System (PQS)**: Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)

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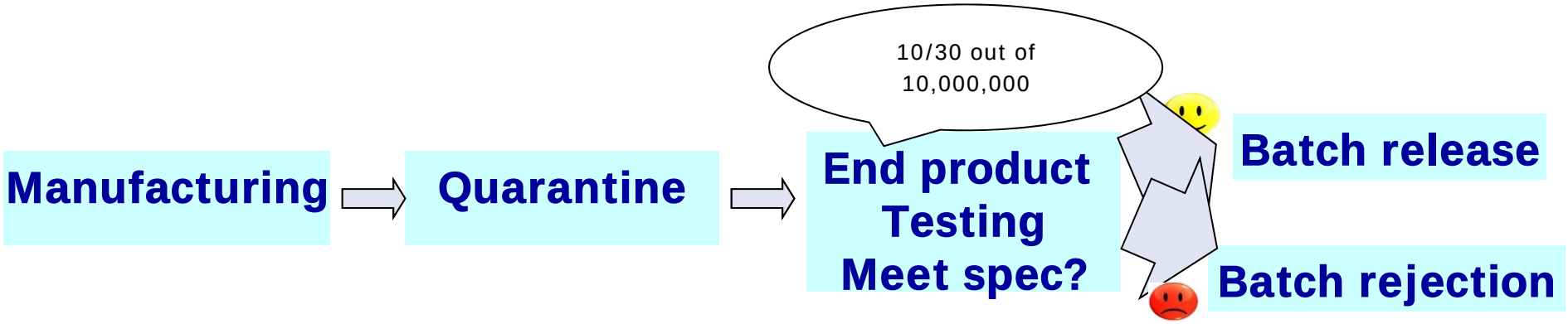
"Quality cannot be tested into products; quality should be built-in by design".

https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm128080.htm

Old paradigm: ***Quality by End-product testing***

A **relatively old paradigm** of producing medicinal products, which consists of the following four-step sequential process:



- Product quality is checked at the end of the manufacturing process "after the fact"

Yes/No outcome
No possibility for adjustments

Quality by testing- limitations

This approach ignores real-world variability in materials and process controls resulting in slower time to market, cost over-runs and unproductive delays.

When a failure is observed, defective products have already been produced and the cost of poor quality in terms of scrap, rework or warranties is increased.

Studies[i] show that

- The industry average for both rework and discarded product is 50%,
- On hold product inventories are on average 40-60 days,
- Plants work at 40-50% of their capacity,
- Average cycle times are in the 30-90 day range,
- Laboratory tests can add as much as 75% to the cycle time

[i] A. Smith and R. Martin. Pharmaceutical Quality: Build it into the process. AMR research report. May 12 (2004) http://www.pharmamanufacturing .com/ articles/2007/119.html

How can we improve the current state?

W.E. Deming's Quality, Productivity, and Competitive Position (1982) :

"…To accomplish this you must **understand your processes** so well that you can **predict the quality of their output from upstream activities and measurements**…"

Need for a shift in paradigm:

From compliance

to enhanced product and process understanding

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Approaches to pharmaceutical development

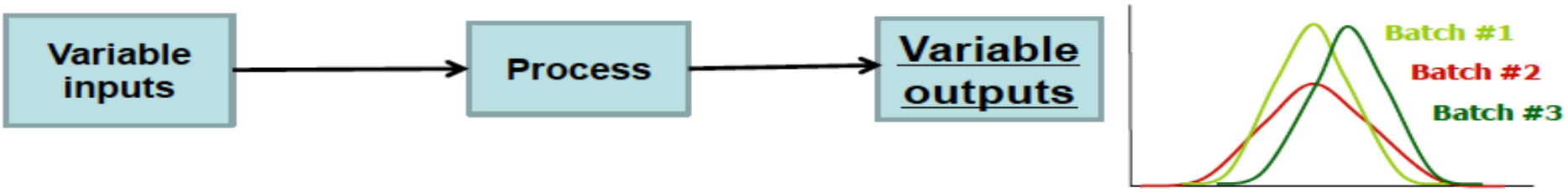
Minimal or Traditional approach	Enhanced QbD Approach
- Empirical - Conducted one variable at a time	- **Systematic** (understanding linkages between material attributes and process parameters that have an impact on product quality) - Multivariate experiments
- Fixed manufacturing process - Focus on optimisation and reproducibility	- **Adjustable manufacturing process** within the Design Space - Focus on control strategy and **robustness**
- Control strategy based on end-product testing and off-line analysis	- **Risk-based control strategy** - Quality control **shifted upstream** into the process -Real time release*
- Specifications: primary means of control	- **Specifications: part** of the overall quality control strategy
- Reactive lifecycle management (i.e. problem solving and corrective action)	- **Preventive** action - Process operations tracked to support **continual improvement** post-approval

➢ **Both** approaches are acceptable, the usual situation is **somewhere in between**

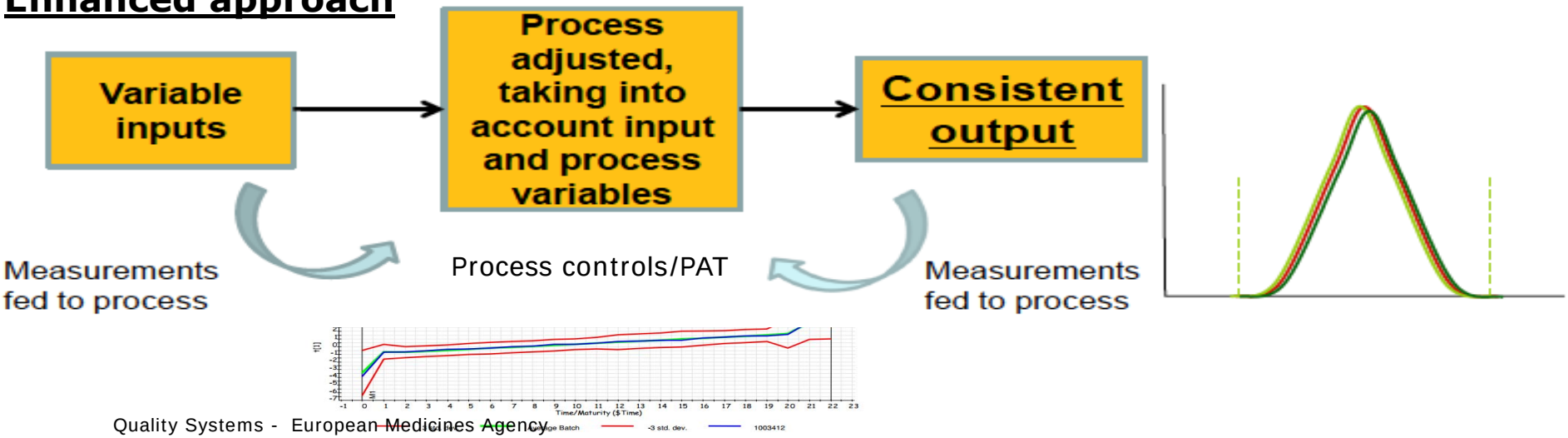
➢**QbD** is preferable as it implies:

- ↑ Knowledge of product/process
- ↑ Control of variability
- ↓ Batch failure and costs
- ↑ Flexible regulatory approaches

Traditional approach

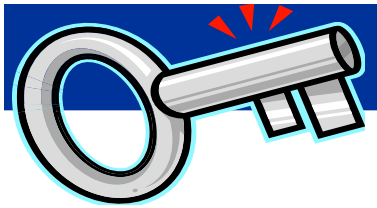


Enhanced approach



Why QbD?

- ✓ Higher level of assurance of product quality
- ✓ Cost saving and efficiency for industry & regulators
  - Reduce cost/product rejects
  - Increase manufacturing efficiency
  - Facilitate innovation
  - Minimize/eliminate potential compliance actions
  - Regulatory flexibility: Streamline post-approval changes & regulatory process
  - Opportunities for continual improvement



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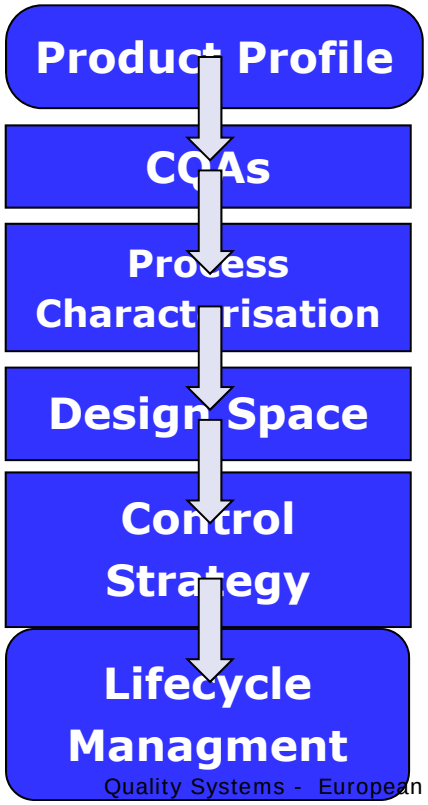
Key elements of QbD approach



QTPP – Quality Target Product Profile

Determine potential **Critical Quality Attributes**

Link material attributes and process parameters to CQAs - **Critical Process Parameters (CPPs)**

Develop a **Design Space** (*optional not required*)

Design and implement a **control strategy**

Manage product lifecycle, including **continual improvement**

Quality Risk Management

Benefits from QbD approach

QbD → better process and product understanding →more robust process

Less batch failures and batch recalls

Minimise out of stock situations

Opportunities for more flexible regulatory approach (Design space, RTRt)

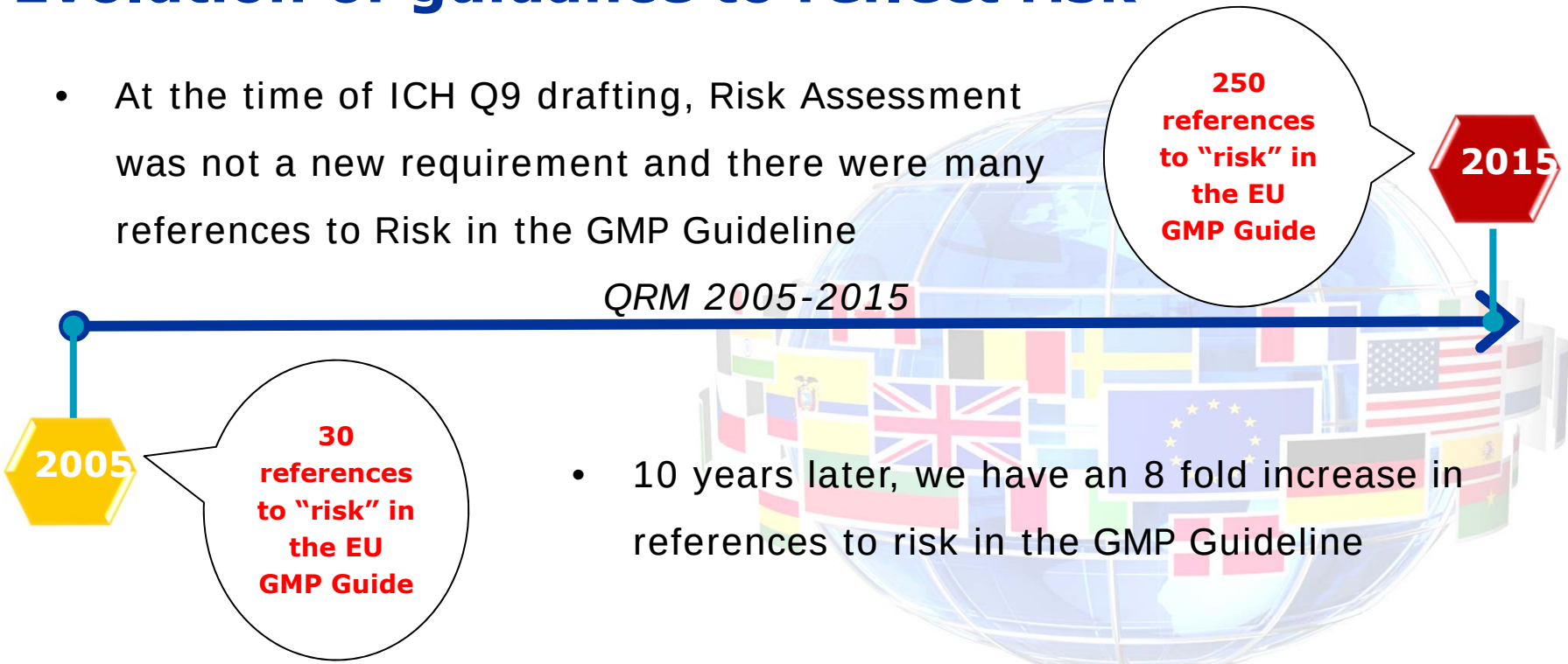
Benefit to the Patient-Industry Regulators

WIN-WIN-WIN

2. How have regulators and the industry adopted Quality Risk Management since 2005?

Evolution of guidance to reflect risk

- At the time of ICH Q9 drafting, Risk Assessment was not a new requirement and there were many references to Risk in the GMP Guideline



- 10 years later, we have an 8 fold increase in references to risk in the GMP Guideline

ICH Q9 - <10 Years on

- Following adoption of ICH Q9 in Nov. 2005, the EU GMP has gone through significant changes to harmonise and incorporate the principles of QRM
- ICH Q8, Q9, Q10 and Q11 resulted in major efforts to modernise the EU GMP and reflect risk-based concepts in almost all areas
- ICH Q9 is a regulatory framework that empowers organisations to make science-based decision making in a wide range of areas
- ICH Q9 applies to both Industry and Regulatory Authorities

QRM in EU GMP Guidelines (I)

Part I (Finished Products)

- **Chapter 1 Pharmaceutical Quality System** (July 2008): QRM required to be an element of the PQS and a link is made to ICH Q9
- **Chapter 3 Premise and Equipment** (March 2015): The measures to prevent cross-contamination should be commensurate with the risks. QRM principles should be used to assess and control the risks.
- **Chapter 5 Production** (March 2015): The level of supervision (of suppliers of starting materials) should be proportionate to the risks posed by the individual materials.
  - *Guidelines on the formalised risk assessment for ascertaining the appropriate GMP for Excipients of medicinal products for human use (March 2015)
  - **Chapter 8 Complaints & Product Recalls** (March 2015): The concepts of QRM and risk assessment, risk-based decision making and risk-reducing actions were introduced.

QRM in EU GMP Guidelines (II)

Part II (APIs) (July 2010) was revised to introduce the QRM principles.

Part III (for Finished Products)

- **Annex 11 Computerised Systems** (June 2011): As part of a risk management system, decisions on the extent of validation and data integrity controls to be based on a justified and documented risk assessment of the computerised system.
- **Annex 15 Qualification & Validation** (Oct 2015): The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly
  any risk assessment activities

Questions and answers on GMP

http://www.ema.europa.eu/ema/index.js
id=WC0b01ac05800296ca%20-%20sectio

QRM for Regulatory Authorities

- The EU Quality Manual for EU GMP Inspectorates updated to incorporate QRM principles in their quality systems
- QRM has a direct applicability for inspections and assessment activities
  - Inspection Planning (frequency, intensity, resource allocation)
  - Assessment of findings and CAPAs following inspections
  - Assessment of Quality Defects, CAPAs and any market action
  - Risk Based Market Surveillance Testing

Issues noted during Inspections

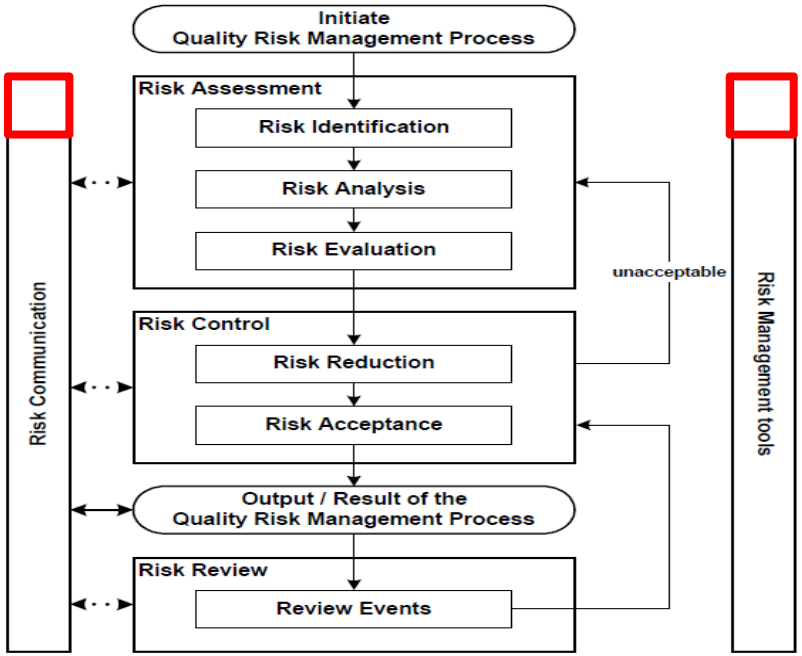
- Increasing use of risk assessment and QRM activities by industry
- Four key problems noted during inspections about risk assessment and QRM
  - **Lack use of good science** (historical data, modelling data, preventive controls, assumptions regarding severity and detection not supported by data)
  - **Lack of rigour in applying the methodology** (using risk question that are too high level, or not specific for the objective, focusing on too many failure modes and only treating them superficially or subjectively)
  - **Poor management of knowledge** (overlooking or ignoring existing and sometimes key knowledge during risk assessments)
  - **Overuse of formal risk assessments** (many issues managed through the formal risk assessments, sometimes formal but flawed risk assessments provide a sense of security in decision making)

Source: Kevin O'Donnell "QRM in the GMP Environment: Ten Years On—Are Medicines Any Safer Now? A Regulators Perspective", QUALITY RISK MANAGEMENT, Journal of Validation Technology 2016.

Global GMP Issues – EMA Perspective

- **Non-compliant sites due to basic GMP failings**
  - Data Integrity, Sterility issues and Risk of Contamination accounted for **85%** of the findings that led to GMP Non-Compliance in 2016.
- **Product recalls, potential or actual shortages due to manufacturing and quality problems;**
  - Lack of supply chain resilience;
  - Lack of proactivity in risk-assessment and risk mitigation measures;
  - Reduction in manufacturing capacity with no alternatives registered in Marketing authorisation.
- **Known problems in development getting through to commercial manufacturing: failures in technology transfer**
  - Lack of continuous improvement;
  - Lack of investment;
  - Poor quality interactions / communication between the industry and the regulator.

Quality Risk Management: ICH Q9 – The Process



QRM is implemented properly if these are all present:

1. Risk **Assessment/Control/Communication/Review**
2. Integrated into the **QMS/PQS**
3. Systemic process for **QRM**
4. Ultimately linking to **patient safety**
5. Based on **scientific knowledge** and **experience** with the process
6. Level of **effort**, formality and documentation is **commensurate** with level of risk
7. QRM is a **lifecycle effort** and requires **vigilant management** of risks

Source: Ian Thrussell, "QRM – An enabler in the QMS and product life cycle".

Using QRM to Improve Quality

- More QRM competencies development through training and knowledge management
- Effective risk assessments based on good science and robust data (data integrity is key)
- Shift focus from reactive to proactive risk management and more explicitly assess supply chains and transport risks as part of procurement and contract management and corporate governance processes
- Improve *pre*- and *post*-incident communication on disruptions
- Develop supply chain resilience

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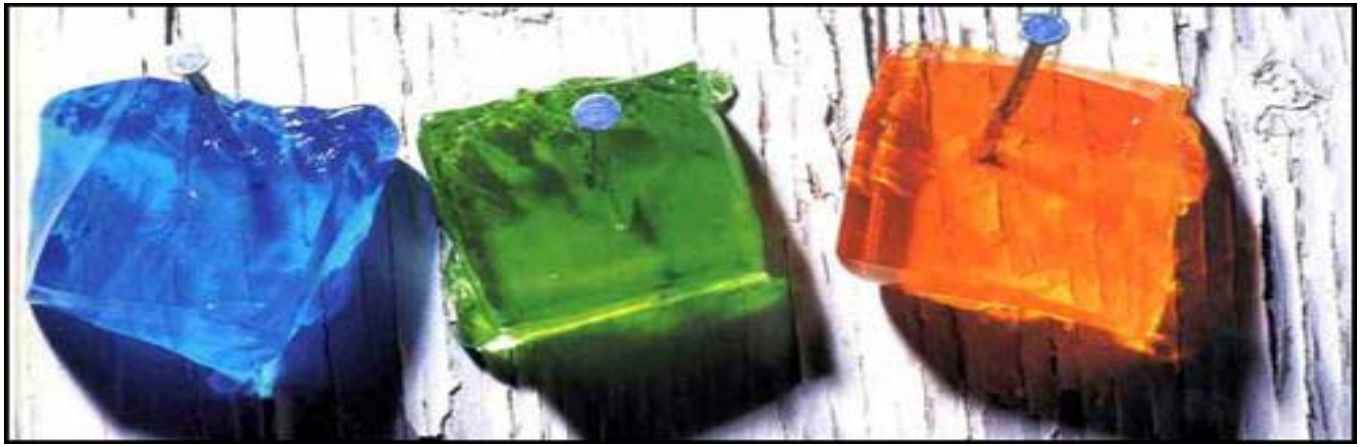
3&4. Current concepts of quality systems & Quality System Indicators and Tools to evaluate GMP compliance

Quality Culture is intrinsic to a Quality System



Indicators of mature Quality Culture:

- Led from the top, empowered from below
- Communication of priorities
  - To personnel
  - To shareholders
  - To clients
  - To regulators
- Relevant monitoring
  - Critical review of what metrics are monitored, and the environment in which they are being monitored.

Metrics: careful selection

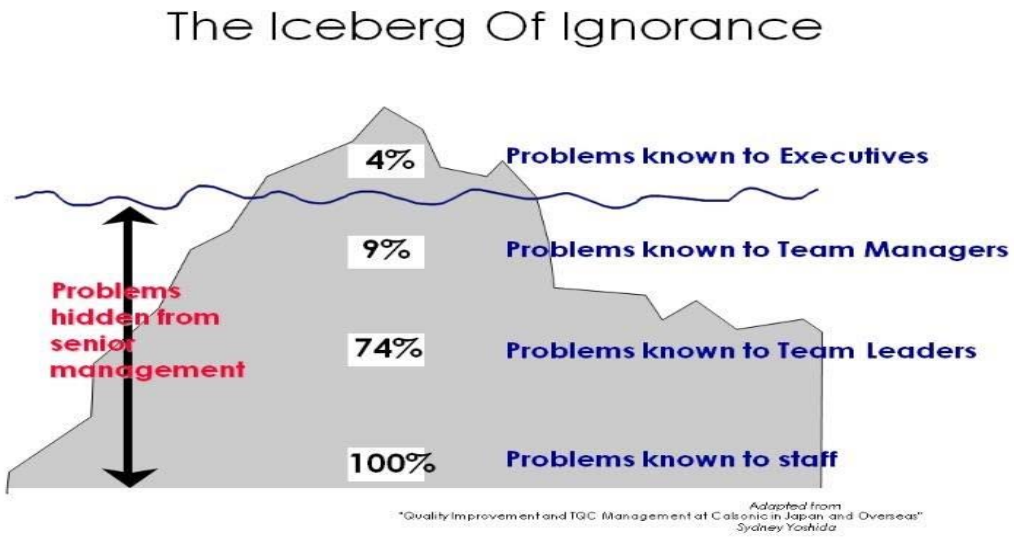
- Careful selection of metrics is required
  - What behaviours do the metrics demonstrate?
  - What behaviours do the metrics influence?
  - What is the relevance of each metric to product quality or patient safety?

"The only true measures of quality are the outcomes that matter to patients"

Michael E. Porter and Thomas H. Lee, MD
Harvard Business review October 2013.

Metrics: careful selection

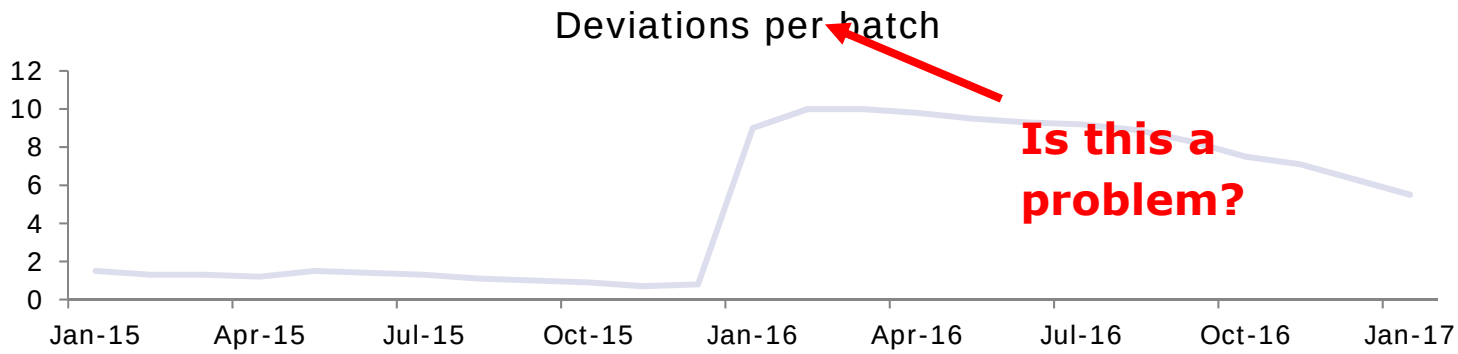
- Is the company monitoring the right things?
  - NOW
  - IN FUTURE



The Guardian commercial - Points Of View (360p).mp4

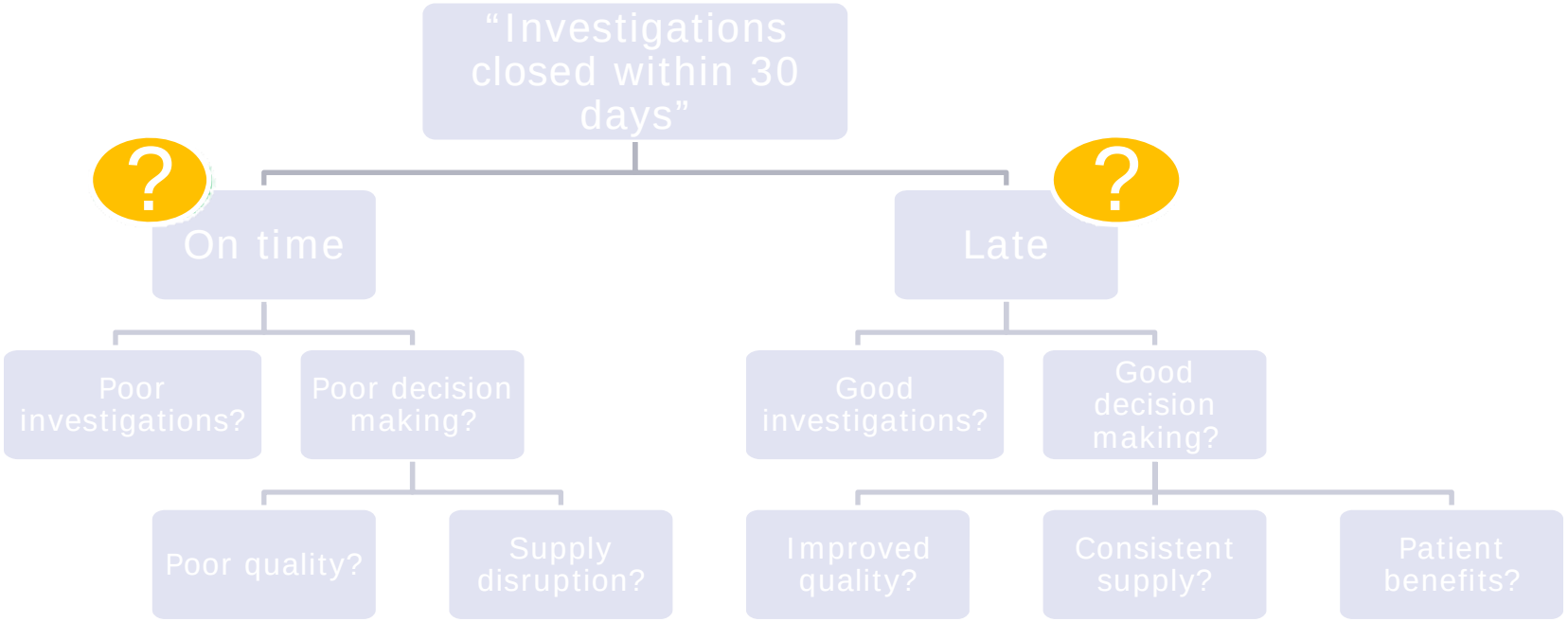
Metrics: careful assessment

- The need for context is paramount when interpreting metrics



- Metrics which give context are as important as the metrics themselves

The importance of context



Applicable to all key Quality System Components

- Change controls
- Document changes
- Deviations / Non conformances
- Complaints
- Recalls / Returns
- Adverse event and reaction reporting

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Pharmaceuticals

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Procedures Related to GMP Inspections

A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers

Table of contents:

Title	**A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers**
Date of adoption	June 2013
Date of entry into force	1 December 2013
Supersedes	version of the procedure adopted in Nov 2007, EMA/INS/GMP/321252/2012
Reason for revision	Updated to incorporate the PI-037-1-PIC/S Recommended Model for Risk-based Inspection Planning in the GMP Environment
Notes	

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- T…

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Product Quality Review
(inter alia)

- Supply chain traceability of active substances
- OOS and trending
- deviations / non-conformances
- Changes to processes and/or analytical methods
- MA variations
- Stability monitoring results
- Quality-related returns and complaints
- Corrective actions

Conclusion

- Understand difference between Quality by design and a Robust Pharmaceutical Quality System
- Quality Risk Management and its importance to regulators and industry
- Brief Overview of Quality System Indicators and Tools to evaluate GMP compliance

Thanks

- EMA Quality Colleagues – Delores Hernan / Brian Dooley
- EMA Manufacturing and Quality Compliance Colleagues – Andrei Spinei / Maria Filancia
- MHRA friends – David Churchward

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Any questions?

Further information

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Back Up Slides

Additional Guidance QbD

- ICH Q-IWG Q&A and Points to consider

  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/Q-IWG_Q_A_R4_Step4_Nov.2010.pdf

  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtCR2_6dec2011.pdf

- QbD EMA webpage

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000162.jsp&mid=WC0b01ac058076ed73

- Joint European Medicines Agency/Parenteral Drug Association QbD workshop

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/12/event_detail_000808.jsp&mid=WC0b01ac058004d5c3

Additional Guidance QbD

- Guideline on **Real Time Release Testing** (formerly Guideline on Parametric Release) EMA/CHMP/QWP/811210/2009

  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125401.pdf

- Guideline on the use of **near infrared spectroscopy** by the pharmaceutical industry and the data requirements for new submissions and variations EMEA/CHMP/CVMP/QWP/17760/2009 Rev 2

  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167967.pdf

Additional Guidance QbD

- Guideline on **process validation for finished products** – information and data to be provided in regulatory submissions EMEA/CHMP/QWP/BWP/70278/2012-Rev1 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162136.pdf
- **Draft** Guideline on **process validation for the manufacture of biotechnology-derived active substances** and data to be provided in the regulatory submission

  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165805.pdf
- Post Approval - EU variation system / **Variations guideline** http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:223:FULL:EN:PDF

Future perspectives for QbD

- ICH Q12 Guideline: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

  In progress - step 1 Concept paper published

- Implementation of QbD :

To discuss your QbD submission in EU:

- Contact the PAT Team (qwp@ema.europa.eu)
- Seek formal scientific advice (scientificadvice@ema.europa.eu)