

ICHQ8, Q9 & Q10

Challenges and opportunities A GMP Inspector's perspective

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Presentation overview

- Why do EU Regulators and Inspectors already take such an interest in a company's QMS and QRM plans
 - what do we find?
- Current EU and National positions and initiatives
- Potential benefits of robust Quality Systems
 - Q10 and Q8, Q9, Q10 together, for both Industry and the regulator
- Concerns and challenges to successful outcomes

Current regulatory and external environment



- Fundamental issue is patient safety – availability of products of appropriate quality
- Perceptions of the industry and its environment:
 - Regulatory processes inflexible
 - Innovation and improvement stifled
 - Risk averse compliance focus with non-science or non risk-based regulations and guidance – lack of risk appetite
 - Toleration of the status quo

Issues still occur despite regulations, guidance, standards, training, communication, inspection and enforcement:

- **Serious manufacturing issues:** Chiron influenza vaccine contamination
- **Serious control issues:** recent Foot and Mouth Disease
- **Cross contamination issues** – glycerol, heparin, mix ups
- **Unexpected events:** TGN1412 (Northwick Park incident)
- **Criminal activities:** counterfeiting
- Lessons being learnt!

- ICH discussions in July 2003 (Brussels) for agreeing a consensus vision : “Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to risk management and science”
- From this vision, elaboration of new ICH guidance :
 - Q8 : Pharmaceutical Development plus ICH Q8 R
 - Q9 : Quality Risk Management
 - Q10 : Pharmaceutical Quality System.

The *vision*. *Systems that.....*



- **Leverage knowledge** and encourage a preventive action culture, which ensures that actions are taken before a problem / issue arises
- **Improve quality monitoring and review** (e.g. data evaluation, statistical process control and process capability measurements), which form the basis for continual improvement of processes
- Provide **greater assurance** that there is **no unintended consequence** as a result of continual improvement activities
- Are **widely accepted** globally.

ICH Quality Initiatives

*Pharmaceutical
Development:
Quality by
Design*
Q8

+

*Quality Risk
Management*
Q9

+

**Modern Effective
Pharmaceutical
Quality Systems**
Q10

A red bracket spans across the three quality initiatives (Q8, Q9, and Q10) above it.

Lower Risk Operations
Innovation and Continual Improvement
Optimized Change Management Process
Flexible Regulatory Approaches

- Q8 with (in)famous DS and still more (in)famous QbD :
- Are these concepts really new or formalization of existing concepts ?
- QbD discussed for years without an agreed definition of this concept ?
- How do we talk about “regulatory flexibility” when specifications of the DS are agreed in the Marketing Authorisation ?

- Q9 which is unique as for industry **and** regulators :
 - Harmonised implementation within the EU (e.g. Q9 implementation group at the EMEA level for GMP related matters or working group of assessors)
 - Is optional but is not an open door to think that the EU legislation could also be optional
 - Already assessed by EU GMP inspectors with some good experiences and also lot of bad

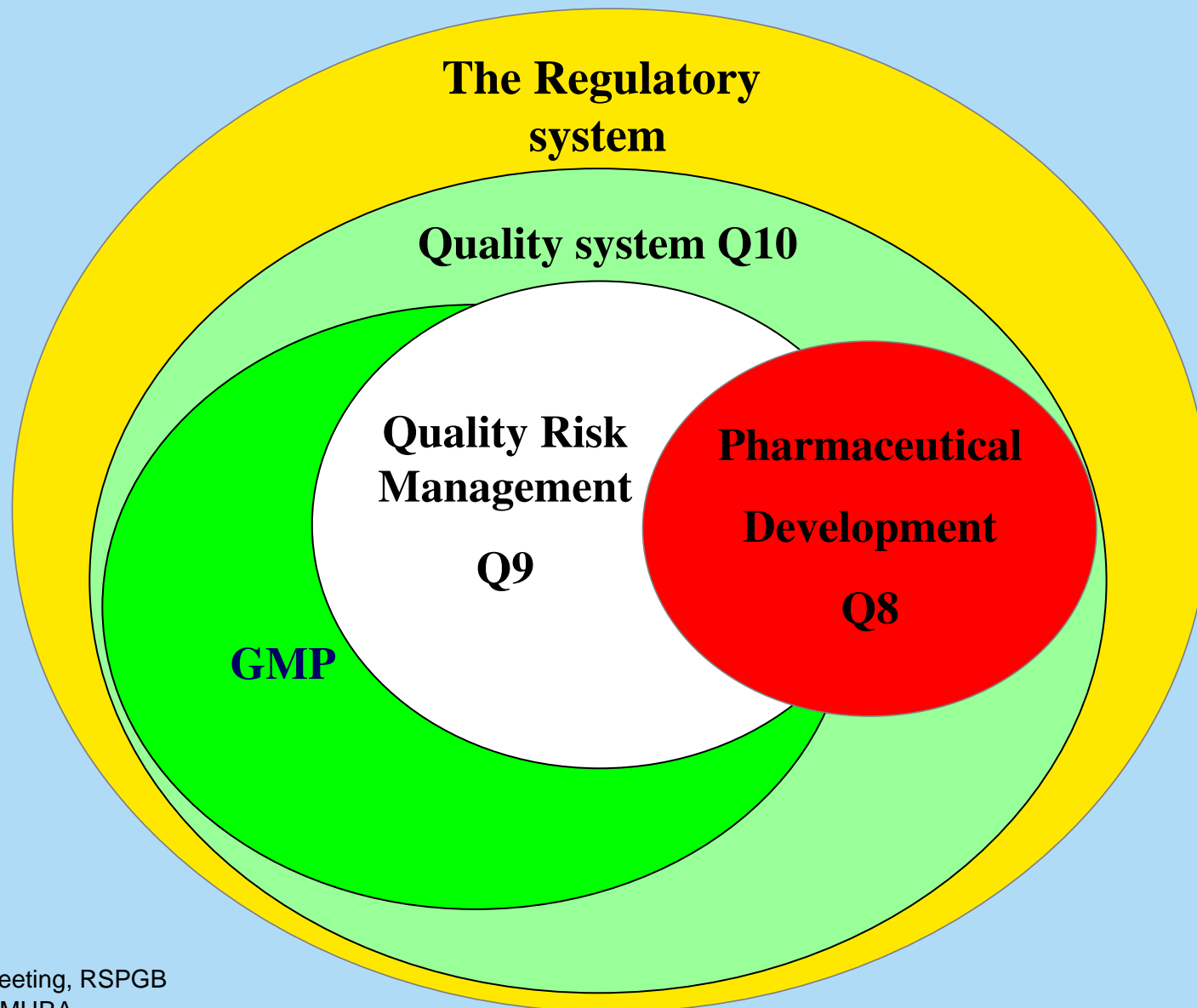
- Q10 which should be an ideal tool to assist in the good implementation of Q8 and Q9 :
- Derived from ISO norms which will facilitate implementation

Is not based on science

Should be carefully considered as it concerns all the lifecycle of the products. Implementation might be difficult at certain stages of the life cycle

- Using concepts described in ICH Q8, Q9 and Q10, there are opportunities for “regulatory flexibility” on process and product through information (and knowledge?) transfer between Industry and Competent Authorities.
- But even for this often quoted “regulatory flexibility” Does everyone know and agree what it is really

PQLI fundamentals – system relationships



- EU position
 - EU MA application procedures have always allowed for a company to demonstrate its knowledge and process for a product's development
 - An effective QMS is already mandated by EU GMPs and most of the accepted common elements of an effective QS are already required by EU GMP.
 - Risk management is implicit in the current GMP guide but will be more explicit with the additional text to Chapter 1.
 - Assessments & inspections conducted into company risk assessments, QMs for many years but looking at QRM processes is newer.

What's the current regulatory and external environment that the Inspector works in?



GMPs are a widely accepted as being a critical element of an effective Pharmaceutical Quality System **but**:

Regional GMPs do not currently apply across all life cycle but:

- GMPs do provide guidance on manufacture and control of pharmaceutical products
- GMPs do provide guidance on most of the essential elements of a Quality Assurance System
- GMPs address CAPA but not proactive continual improvement
- GMPs touch on management responsibilities

GMPs do not address the systems needed to bring a quality product to market and fully manage post marketing change.

We do GMP – what have we to learn from ISOs?

Why do EU inspectors already look at an organisation's QMS and QRM programmes during inspections?

- Why would a company want to do it any other way?
- ***Looking at how companies react when things go wrong and are under pressure is a major diagnostic indicator of the robustness of the scientific and organisational integrity of a company's operations***
 - Do they investigate to improve knowledge or simply build arguments for release of product
 - Quality of investigations- appropriateness of depth of investigation
 - Reactive rather than proactive usage
 - Quality is everyone's responsibility – Is this true when things go wrong?

QRM - Currently – industry application areas



- Current use is largely reactive:
 - on sites when there are significant problems
 - use structure and formality to get to root cause(s)
 - provides guide to rank issues
- Evaluating a company's response when things go wrong is a major diagnostic indicator of the robustness of the organisation's systems and culture

- Proactive use during:
 - development: selection of product / process, studies to conduct, data to be submitted in CTA / MAA, specifications in PSF
 - IMP/commercial: protection product / environment; choice of facility/equipment type; depth of validation of facilities/equipment, process, cleaning, IT; location / method / extent of EM; supply chain evaluation; training; change management systems; quality incidents systems

QRM fundamentals – Competent Authority application areas

- European Commission:
 - Better Regulation launch in 2002
 - simplify and improve regulatory environment
 - impact assessments, consultations
- Changes to Compilation of Community Procedures
 - facilitate approaches to regulatory inspections
 - proposes baseline inspection time on different sites
 - aim is to establish common ground
 - no conflict with QRM/Better Regulation
- Updates to the EU GMP Guide – Chapter 1 and Annex 20

- “Better regulation of pharmaceuticals: towards a simpler, clearer and more flexible framework on variations”
 - focus on the changes having a genuine impact on quality and further reduce the overall number of variations
 - regulatory action classified according to relative risk
 - applies to Community and National Licences
 - design space optional but encouraged
 - continuous improvement encouraged
 - Type 1A - do and tell procedures: annual reporting or immediate notification (admin procedures)
 - Type 1B by default

Why do organisations conform?:

Knowledge, belief, support and a fear of retribution!

- Knowledge of the requirements or regulations
- Costs of compliance/benefits of non-compliance
- Loyalty and natural obedience of the regulated firm
- Degree of collective business and popular acceptance of the desirability of the guidance and/or regulation to deliver its expected outcomes
- Extent of self-monitoring
- Probability of report through self-monitoring
- Probability of inspection
- Probability of detection
- Selectivity of the inspector
- Chance of sanctions
- Severity of sanctions

- ‘Reducing administrative burdens: effective inspection and enforcement’, March 2005
- Executive summary:

“**Risk assessment** should be comprehensive, and should be the basis for all regulators’ enforcement programmes. Proper analysis of risk **directs regulators’ efforts at areas where it is most needed**, and should enable them to reduce the administrative burden of regulation, while maintaining or even improving regulatory outcomes.”

- Principles:
 - allow & encourage economic progress, intervene only when there is a clear case for protection
 - comprehensive risk assessment to focus resources
 - no inspection without a reason
 - provide authoritative, accessible advice
 - businesses not have to give unnecessary information
 - quickly identify businesses that persistently break regulations, face proportionate and meaningful sanctions
 - regulators accountable for their efficiency and effectiveness, remain independent in decisions taken

Regulatory changes – UK: Better Regulation



- Not 'no' regulation!
- Wide range of UK regulators in scope
- Statutory Code of Practice: the Regulators' Compliance Code
- Legal enabler for the Hampton Principles
- BRE/NAO 'reviews' of the Principles are in progress
 - 6 key areas:
 - Focus on outcomes
 - Advice and guidance
 - *Risk based inspections*
 - Design of regulation
 - Data requests
 - Sanctions
- MHRA to be 'reviewed' during 2008

Regulatory changes – UK: MLX 345 on ‘risk-based inspection programme for good practice inspections’

- Public consultation closed 15 Jan 08
 - provides background and general approaches
 - starter questions invite responses
 - link to introduction of daily fees (MLX 344, <9 Jan 08)
- Process not event:
 - phased implementation
 - ‘risk appetite’ in pharmaceuticals is different to many other regulated areas [FSA - ‘the level of harm or failure which one is prepared to accept’]
 - consequences will directly affect the health of large number of individuals

- Trust and culture change:
 - Clear understanding of stakeholders needs and options
 - Trust and openness in working and learning together
 - Culture change:
 - Overcome internal conservatism and ‘silo’ thinking
 - Organisational change management – resistance to change, new competencies needed

Challenges and opportunities



- Regulatory duty to take into account all kind of companies (global companies. medium and small size, generics etc)
- Must be no disadvantage to those with new approaches, especially first movers, or Small and Medium Enterprises
- Need to clarify and share definitions and understandings to facilitate effective implementation
- Degree of industry comfort with the life cycle approach?
e.g. inspectors may go into Development more often

In summary, how might industry and regulators use Q 10 with Q8 & Q9?

Deliver the potential opportunities for:

- Increased use of risk-based approaches for regulatory inspections
- Facilitated science-based pharmaceutical quality assessment
- Optimized science and risk-based post-approval change processes to maximize benefits from innovation and continual improvement
- Innovative approaches to process validation establish real-time release mechanisms enabled

In summary, how might industry and regulators use Q 10 with Q8 & Q9?

From	To
“Blind” compliance	Science, risk-based compliance
Process validation	Continuous (real-time) quality verification and improvement
Quality by testing	Quality by design

In summary, how might industry and regulators use Q 10 with Q8 & Q9?

From	To
Specifications based on process history	Control strategy developed from process understanding and control
End product testing	Real time assurance of quality
Validation through three consecutive batches pre launch	Ongoing validation through routine manufacture
Focus on reproducibility, ignoring variation	Focus on robustness, controlling variation
Processes locked down, changes require review. Less flexibility in lifecycle management	Flexible process allowing continuous improvement
Quality control	Quality assurance

Conclusion



MHRA:

- Committed to safeguarding public health but with an appropriate level of flexibility.
- Successful implementation requires:
 - effective and robust QRM underpinned by an effective QS
 - trust and culture change
- Committed to fostering innovation: new products, new ways of working, product availability
- Pleased to be consulted and to support initiatives
- Regulators also have finite resources - not possible to go further or faster without them!

And finally:



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Abbreviations

- QRM: Quality Risk Management
- Q8: ICH draft guideline - Pharmaceutical Development, Quality by Design
- Q9 ICH draft guideline - QRM
- Q10 ICH draft guideline - pharmaceutical quality system
- QS Quality Systems
- CAPA Corrective and preventive action
- EM Environmental monitoring
- IMP Investigational Medicinal Product
- PSF Product Specification File
- CTA Clinical Trial Authorisation
- MAA Marketing Authorisation Application

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