



**Reflections about Quality Control and Quality Assurance in Clinical Trials**

*3rd International Summit on  
GMP, GCP & Quality Control  
September 25-26, 2014 Valencia, Spain*

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The complex block contains the Telstar logo in the top right corner. The main title "Reflections about Quality Control and Quality Assurance in Clinical Trials" is centered in a bold, dark blue font. Below the title, the event details "3rd International Summit on GMP, GCP & Quality Control" and "September 25-26, 2014 Valencia, Spain" are presented in a smaller, italicized font. At the bottom right, the website address "www.telstar-lifesciences.com" is provided. A large, abstract graphic of three overlapping blue leaves with white veins is positioned on the left side of the page, partially overlapping the text area.

## Current Environment



- The changing environment in which clinical research is conducted invites new approaches in quality management.
- Legal and regulatory requirements lead to collect information that is valuable to improve the efficiency and effectiveness beyond regulatory compliance.
- The most actual approaches to systems for quality management are based on processes evaluation.
- Evaluating the performance of processes and risk assessment are being introduced in the day to day monitoring and is acquiring an important role in the management systems of quality in clinical research.



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## Challenges of Clinical Research



- Clinical development is a very important part of the investment for the development of a product.
- Economic conditions are changing, forcing revise cost structure.
- Regulations impose new requirements and new management stile for clinical research.



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## Quality Control and Quality Assurance: ICH Requirements



- The **sponsor is responsible** for implementing and maintaining **quality assurance and quality control** systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
- **Quality control** should be applied to **each stage of data handling** to ensure that all data are reliable and have been processed correctly



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## Quality Control versus Quality Assurance (1)



- **Quality control** is an instrument of technical verification, which identifies the level of compliance with the specifications of our products and / or services and to make decisions about them.
- **Quality assurance** is an element of organization and management, designed to ensure the quality of our products and / or services, through a set of pre-established, demonstrable and systematic actions, to provide confidence that the organization can meet predetermined quality requirements.



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## Quality Control versus Quality Assurance (2)



- **Quality Control = Testing and verification**
  - Some times, it is not feasible.
  - When it is feasible:
    - 100% is expensive.
    - Sampling is no sure.
  - Objective: Remove products generated out of specification.
- **Quality Assurance = Proactive and Preventive actions**
  - Examples:
    - Evaluation of supplier.
    - Identification and control of critical points.
    - Processes well defined and capable.
    - Training.
  - Objective: Minimize the risk to generate products out of specification.



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## Quality Control versus Quality Assurance (3)



**Quality Control**



**Quality Assurance**



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## Standard Practices (1)



- **Monitoring:** The act of **overseeing the progress** of a clinical trial, and of **ensuring** that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).
- **Audits:** A systematic and **independent examination** of trial related activities and documents **to determine** whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).



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## Standard Practices (2)



- **Data Management:** Data management begins with the submission of the CRF to the sponsor and includes activities related to handling clinical study data, including database creation, data entry, **review**, coding, data editing, **data QC**, archiving and reporting of the database.
- **Data Validation:** Process used to **determine** if data are **inaccurate, incomplete, or unreasonable**. The process may include format **checks**, completeness checks, check key tests, reasonableness checks, and limit checks.



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## The New Approach



- ICH Q9 (2005): Quality Risk Management
- ICH Q10 (2008): Pharmaceutical Quality System.
- EMA/INS/GCP/394194/2011: Reflection paper on risk based quality management in clinical trials.
- FDA Guidance for Industry: Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (2013).



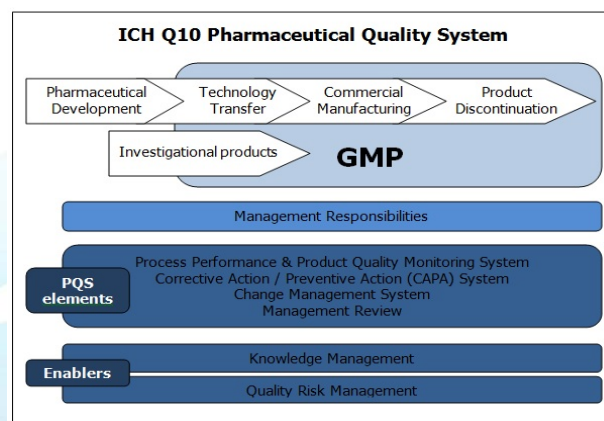
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## ICH Q10 (1)



- ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on ISO 9001 quality concepts, includes applicable GMP regulations.

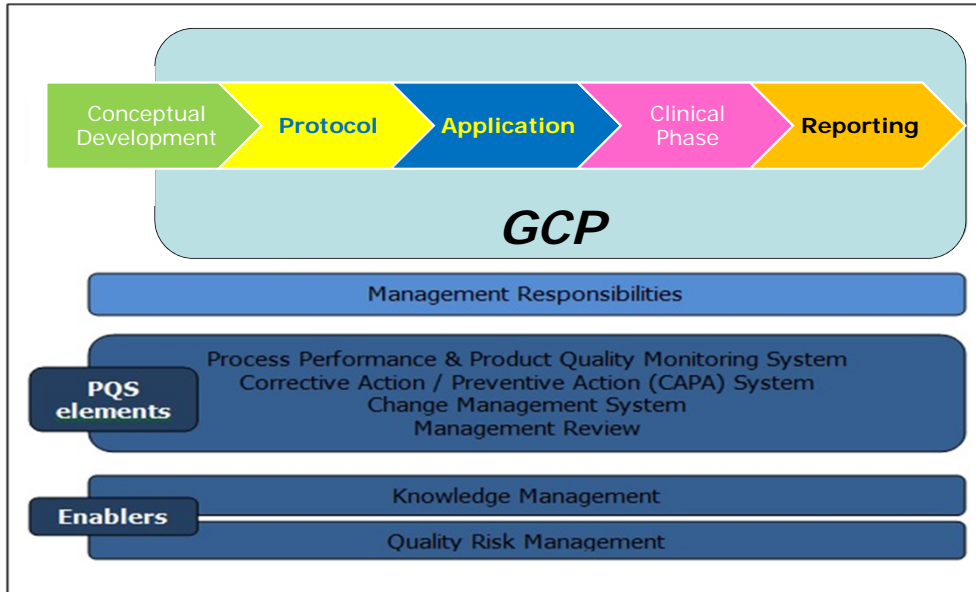
**IS THIS  
MODEL  
FEASIBLE  
IN  
CLINICAL  
TRIALS?**



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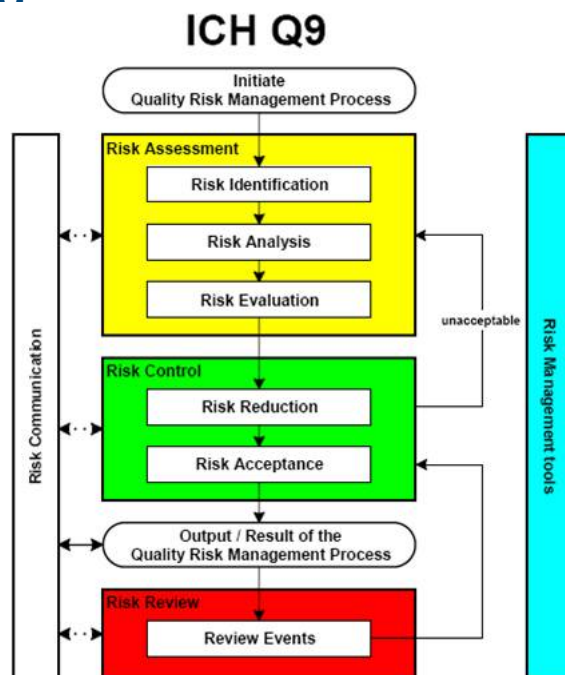


# ICH Q10 (2)



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# ICH Q9



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## Risk Management



- **Risk Management:** Systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling and communicating risk.
  - Risk Assessment: Systematic process of organizing information to support a risk decision to be made within a risk management process.
  - Risk Control: Actions of implementing risk management decisions.
  - Risk Communication: Exchange or sharing of information about risk and risk management between the decision maker and other stakeholders.



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## Questions to answer



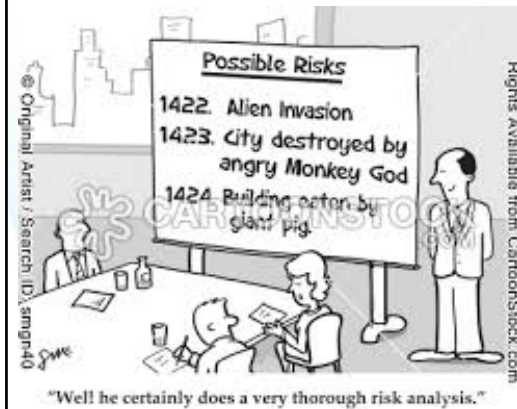
Three fundamental questions to answer:

- What might go wrong?
- What is the probability) it will go wrong?
- What are the consequences (severity)?



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Quality risk management includes systematic processes designed to coordinate, **facilitate and improve science-based decision** making with respect to risk.

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## Quality by Design



- Quality by Design:
  - Scientific, risk-based, holistic and proactive approach to pharmaceutical development.
  - Deliberate design effort from product conception through commercialization.
  - Full understanding of how product attributes and process relate to product performance.

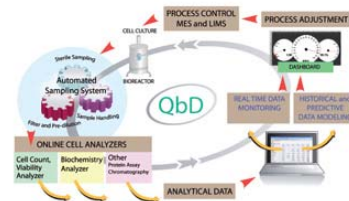


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## QbD In Clinical Trials



- Although this concept comes from the manufacturing area, general principles can be applied in some aspects of clinical trials, as:
  - Protocol.
  - Trial Master File.
- Objectives:
  - Improve quality.
  - Avoid “Trial and error”.
  - Reduce changes.



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## Monitoring



**The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)**

**ICH E6(R1), 1.38**

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## Potential sources of risks



- **Failure to identify priorities**. Both study and process design is often cluttered by data collection requirements or quality control activities of limited importance that distract greatly from the most important issues.
- **Lack of proportionality** in the implementation of quality control activities often related to a lack of understanding of the impact of variability in trial conduct and measurement or data collection on the study results and their reliability.
- **The quality control** steps associated with **monitoring** activities are **poorly described**.



*"Reflection paper on risk based quality management in clinical trials"  
EMA/INS/GCP/394194/2011*

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## Monitoring and QA



**Processes to ensure that root cause analyses are conducted where important deviations are discovered and that appropriate corrective and preventive actions are implemented to address issues identified by monitoring**

*"FDA Guidance for Industry: Oversight of Clinical Investigations  
A Risk-Based Approach to Monitoring"*

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## Corrective and Preventive Actions

- **Immediate action:** Action to mitigate the effect of a deviation or nonconformance.
- **Corrective action:** Action to eliminate the cause of a detected nonconformity and prevent recurrence.
- **Preventive action:** Action taken to eliminate the causes of a potential nonconformity

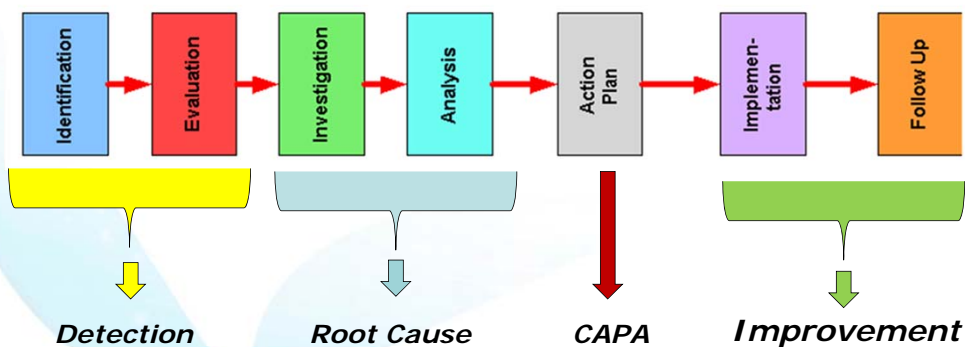
**Are the CRA's trained in this process?**

**Is monitoring planned with this scope?**



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## Exploitation of results



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## Monitoring and audits



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"The availability of meaningful and actual information is a true weakness in QC today."

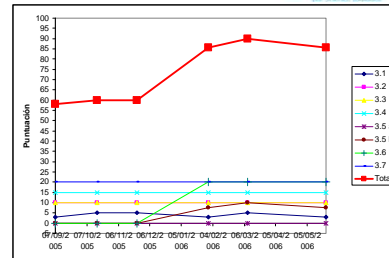
Jeremy Burcham  
AVP of Loan Review Solutions

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## Quantifying the Quality



- **Metric:**
  - Standards of measurement by which efficiency, performance, progress, or quality of a plan, process, or product can be assessed.
  - A measure of an organization's activities and performance, associated to measurement procedure of one or more attributes and a scale to evaluate them.
- **Attribute:** A physical or abstract measurable property, that is common to all elements of a category of entities.
- **Indicator:** A metric that, in a specific study, provides a meaningful signal about some aspect of site performance that affects the likelihood of study success or failure.



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## Quantification and improvement process





1. Identify and assess risk factors.
2. Specify indicators and set acceptable values.
3. Stablish a measurement plan.
4. Measure and evaluate indicator scores.
5. When a problem is detected, generate CAPA.
6. Replace successful indicators and measure the effectiveness of CAPA.
7. Analyze temporal patterns and trends.
8. Based on this analysis, take corrective action.





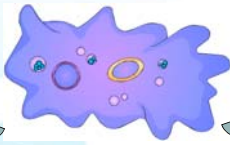
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