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Health Products Regulatory Authority

Session 4: Quality Defect Investigations and Product Recalls

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Outline

- The application of QRM principles to QD investigations
- The HPRA's risk-based approach to QD investigations
  - The Type I QDR process
  - The Type II QDR process
- Market action decision commensurate with risk
- Risk/process review

Applying QRM principles to QD investigations

- GMP Guidelines Chapter 8 - Complaints, Quality Defects and Product Recalls

- ICH Q9: Application of QRM to the identification, evaluation and communication of QDs and to determine appropriate action to mitigate risk

- Compilation of Community Procedures on Inspections and Exchange of Information EMA/385898/2013

Applying QRM principles to QD investigations

- Two primary principles of QRM are:

  - The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient

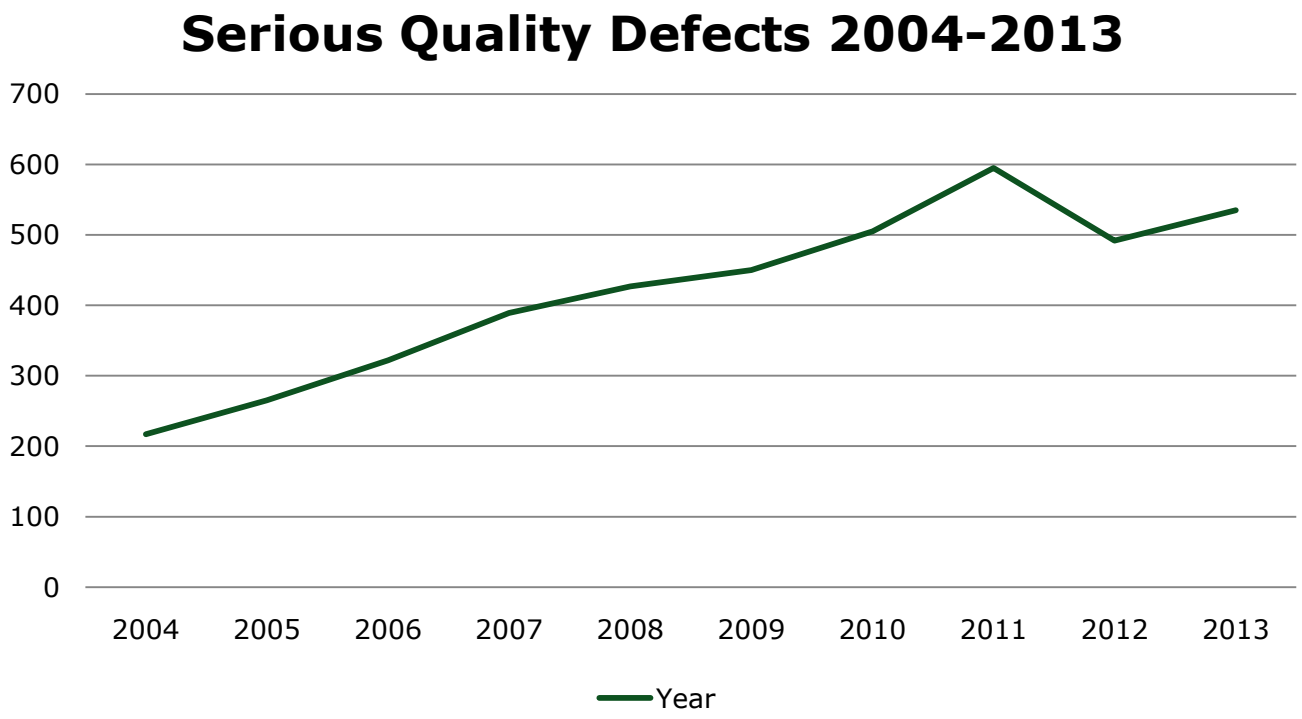
  - The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk

..... ICH Q9

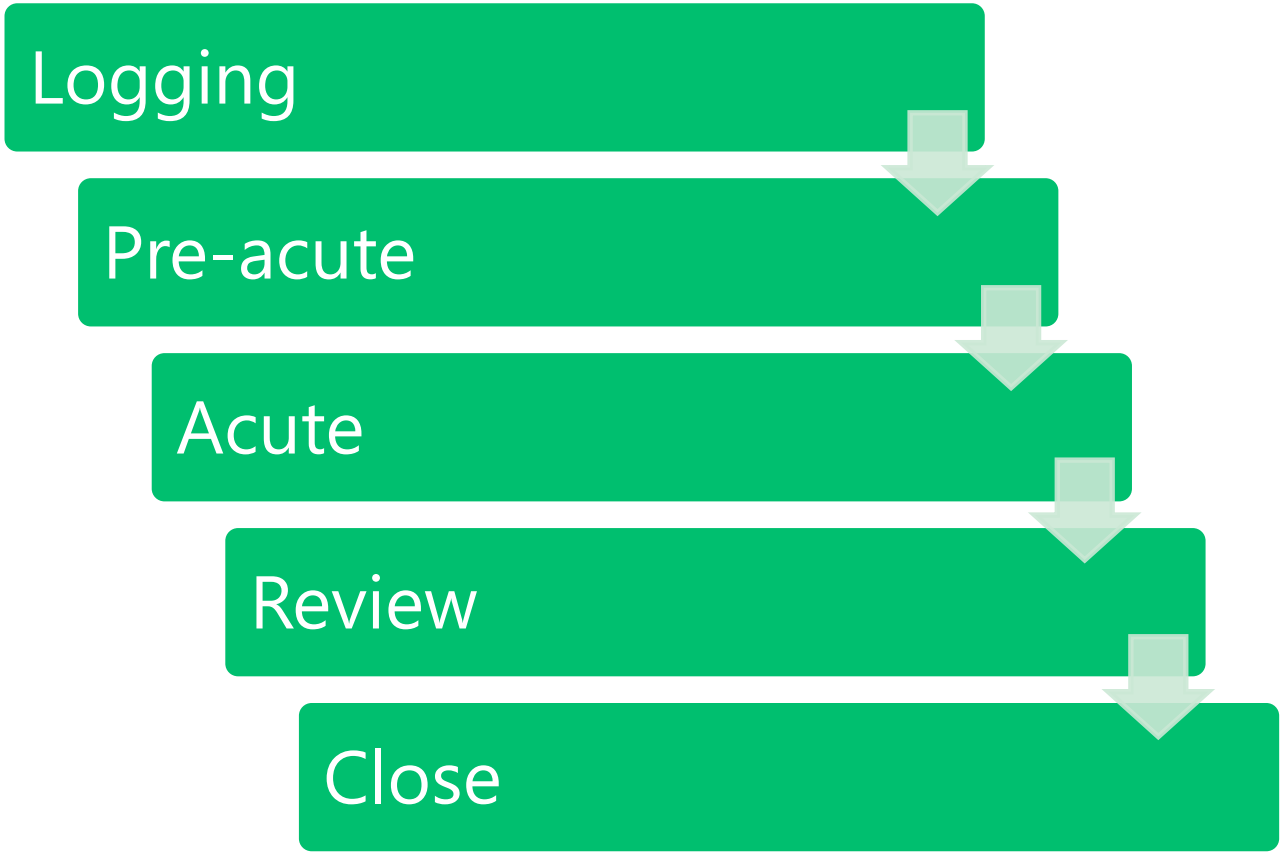
Quality Defects investigated by HPRA 2004-2013

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Critical	50	66	84	173	127	105	173	231	189	235
Major	167	199	238	216	300	345	332	364	303	300
Others	93	62	49	84	128	164	246	322	249	239
Total	310	327	371	473	555	614	751	917	741	774
Recalls	82	74	58	97	141	98	168	253	141	109

Serious quality defects investigated 2004-2013



Overview of QDR process



Applying QRM principles to QD investigations

Receipt of a Quality Defect Report

- Every case is assessed by a Technical Investigator, upon receipt, giving consideration to
    - Information received
    - Scientific knowledge
    - Risk to patient/animal/end-user
- For serious issues, investigation may proceed prior to administrative logging of the QDR

The acute decision-making stage

- Determining whether the QD affects Ireland
  - Manufactured in Ireland?
  - Authorised in Ireland?
  - Distributed in Ireland?

The acute decision-making stage

- Determining whether the QD affects Ireland:
  - Is an Irish-authorised version of the product affected?
  - Is it being placed on the market as an unlicensed product (human) or through the Cascade system (veterinary)?
  - Is there any parallel distribution?
  - Follow up with the reporter/manufacturer/MAH, e.g. CAPs

  - This determination is a high risk part of the process
    - Methodical, proceduralised, input of administrative and technical staff

The acute decision-making stage

- Classify the QD on basis of risk
  - Information-gathering
  - Risk and extent
- Arrive at a decision regarding the remedial actions that are required to address the risk presented by the QD based on information gathered.
  - These include recall action; communication of the issue, e.g. caution-in-use notification; issuance of Rapid Alert, implementation of other remedial actions commensurate with the risk

The acute decision-making stage

Classification	Target (days)
Critical	3 (calendar)
Major	8
Minor	15

Risk Assessment

- **Assessment of the Risk** to the Patient/Animal/End-User
  - Seriousness of the defect
  - Route of product administration
  - Patient groups to which the product may be administered
  - Method of Sale or Supply
  - Detectability of the defect & other risk-mitigating controls

Extent of the defect

- Determine the **extent** of the defect:
  - Number of batches and units affected
  - Other products affected or potentially affected by the same defect
  - How has the extent of the defect been determined?
  - Number of similar complaints against the batch or product from any marketplace

Assessment of Quality Defect

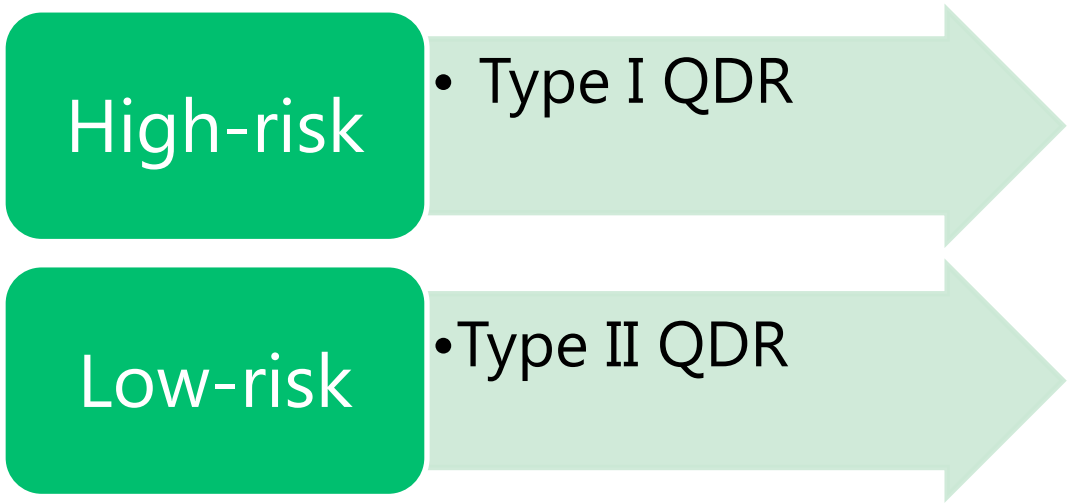
Involvement of interdisciplinary teams as part of QRM:

- Clinical assessment (Human/Vet)
- Pharmaceutical assessment (Human/Vet)
- Pharmacovigilance assessment
- Toxicological assessment
- Inspectors – GDP, GMP, GCP

.....in assessment of risk and decisions regarding market action

Type I and Type II QDRs

- The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk



Type I vs Type II QDR

Logged as either Type I or Type II QDR on the basis of risk

Type II QDR

Only minor or certain major defects	No increased risk posed by the issue	No market action required

Not a Rapid Alert Notification	Not a blood, vaccine or plasma medicinal product

The Type II QDR process

- Procedural requirement to consider upgrade to Type I prior to case completion
- Robust, rigorous process and consistent approach
- All cases discussed by at least two members of QDR team at same forum as for Type I QDRs

The Type II QDR process

Objectives of Type II process:

- "The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk"
- Apply the principles of QRM!
- Continuous improvement initiative
- Workload reduction measure
- Assign resources to high-risk issues

- Pilot project undertaken in 2012 including evaluation of objectives
- Process formalised in 2013

Type I QDRs

All other cases

- All Critical, and most Major, QDs
- All Rapid Alerts
- All cases requiring market action
- All cases concerning blood, plasma and vaccine medicinal products

.....are routed through the Type I process

Market actions

- Remedial actions should be commensurate with the risk as evaluated through risk-based assessment and should take into account the classification, extent of the defect and consultations with relevant colleagues

Recalls from Irish Market in 2013

- 109 recalls (774 QDs)
  - 16% to patient/user level
  - 48% to pharmacy/retail level
  - 37% to wholesale level

- Assessment of risk associated with a recall
  - Potential for out-of-stock situation
  - Criticality of the medicine
  - Availability of alternatives
  - The patient group

When a Caution-in-use Notification is used instead of recalling

Two scenarios

1. When the issue is deemed serious enough to warrant a recall but no alternative replacement product available

2. The issue is not deemed serious enough to warrant a recall and risk can be addressed via a cautionary notice

When a Caution-in-use Notification is used instead of recalling

- A number of cases in 2013 where recalls were desirable but could not be executed at the time as replacement stock was not available

Risk-mitigating measures

- Communications to HCPs to inform them of issue, risk-mitigating actions and to advise them to prepare for recall

Other market actions

Rapid Alerts

- For each Type I QDR, SOP requires that an assessment be made of whether a Rapid Alert should be issued by HPRA

- Risk-based decision with reference to classification of the defect and the Compilation of Community Procedures on Inspections and Exchange of Information

Other market actions

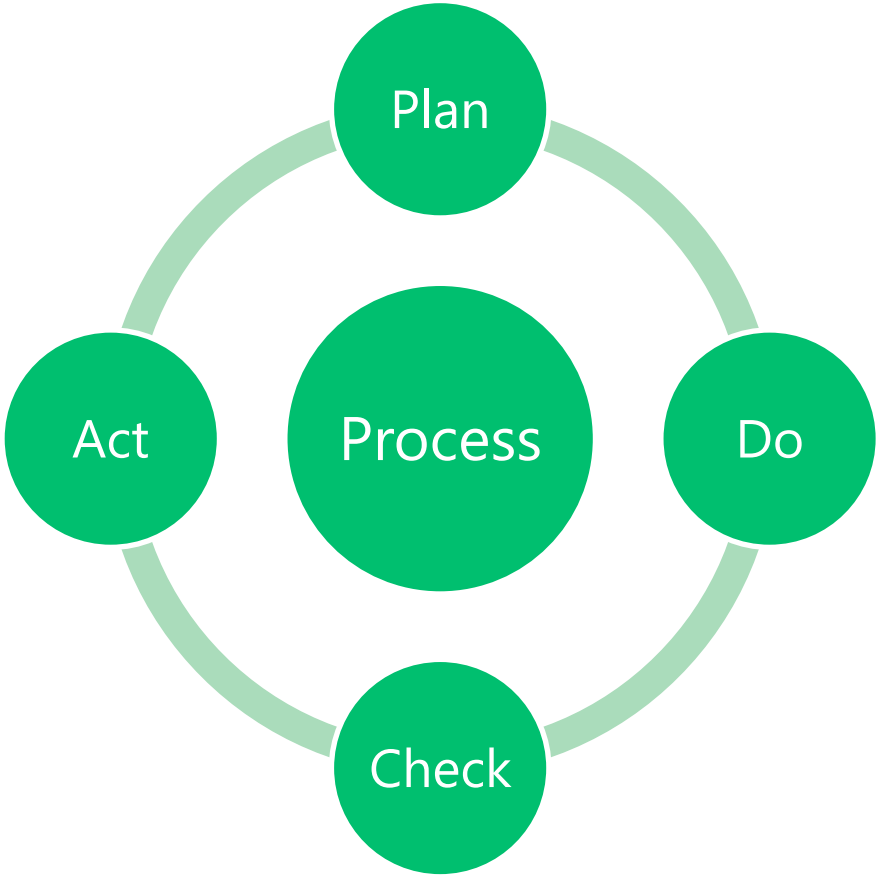
Communications

- Communications to stakeholders, e.g. communication with parallel distributors, wholesalers regarding confirmed falsified medicines issues

Inspection

- QDR issues can lead to for-cause inspections of Irish manufacturing sites – case-by-case and risk-based decision
- Inspection teams kept informed of QD issues affecting Irish manufacturers, wholesalers, MAHs, other relevant establishments to ensure follow-up of issues at next inspection

QRM - Process Review



QRM - Process Review

Process review as part of QRM

- We maintain a program of continuous improvement
- We assess risk associated with continuous improvement initiatives e.g. piloting of Type II process
- Auditing - Internal audit program at HPRA

Summary

- Relevance of ICH Q9 to QDR Investigations.
- Adoption of a risk-based Type I/Type II system to allow resources to be allocated to the high-risk issues
- Case-by-case approach to each QD
- Market actions commensurate with risk
- QRM - Process review

The QDR group at HPRA

Email: qualitydefects@hpra.ie

- **Breda Gleeson** (Market Compliance Inspector)
- **Rob Smyth** (Market Compliance Technical Officer)
- **Amy Kelly** (Quality Defects & Recall Manager)
- **Kevin O'Donnell** (Market Compliance Manager)
- **Louise Bright** (Market Compliance Administrator)

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Thank you

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Revision of Chapter 8 – Complaints & Product Recall

Reasons for Revision…

Significantly out of date - many significant gaps

- No reference to Risk Assessment in relation to quality defects
- No reference for the need for Root Cause Analysis and CAPAs
- No reference to Risk-based Decision Making in relation to quality defects
  - *Emphasis was mainly on product recalls*
  - *No reference to other potential risk-reducing actions*
- The text needed to be strengthened to provide for better investigations and more effective CAPAs
  - *Recurring problems seen by CAs, such as, companies overly assigning human error as a cause and retraining as the CAPA without good justification, needed to be addressed*

Revision Milestones

Working Group set up in 2011 (IMB Rapporteur)

- Concept Paper published June 2011 for public comment
- Some comments received – most showed strong industry support for the proposed revision
- Redrafting started late 2011
  - *Draft Revision sent to Inspectors Working Group in early 2013*
  - *Public Consultation on Revised Draft mid-2013*
  - *Stakeholder comments received and considered*
  - *Revisions made in Q4 2013*
  - *Revised Version sent to Inspectors Working Group Feb 2014 & Adopted*

– *Commission Q2 2014, Adopted & comes into effect* March 1st, 2015

Key Changes… Structure

Total rewrite and restructuring of Ch 8

- New Title: ***Complaints, Quality Defects & Product Recalls***
- Significantly more guidance now included
  - *Principle*
  - *Personnel and Organisation*
  - *Procedures for handling and investigating complaints including possible quality defects*
  - *Investigation and Decision Making*
  - *Root Cause Analysis and CAPAs*
  - *Product Recalls and Other Potential Risk-reducing Actions*

– *Reference to MA non-compliances/unplanned deviations (see Principle)*

– *Improved clarity about when defects should be reported to CAs*

Key Changes… Procedures

Much more detailed guidance on what should be in quality defect procedures

8.9 Procedures should address:

- 8.9ii: The determination of the extent of the quality defect. The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production … and distribution records
- 8.9iii: The need to request a sample, or the return, of the defective product from the complainant…
- 8.9iv: The assessment of the risk(s) posed by the quality defect, based on its severity and extent
- 8.9v: The decision making process concerning the potential need for risk-reducing actions in the distribution network, such as batch or product recalls, or other actions.

Key Changes… Focus on QRM

Significant emphasis on QRM throughout…

- Not just when assessing risk to patients and animals
- Or when making decisions about potential market actions

But also… using QRM to determine the degree of investigation/action

- 8.10: When investigating quality defects…
  - e.g. How much effort to spend on determining the extent of the issue and its root causes should be commensurate with the risks presented by the defect
- 8.10 When determining what CAPAs are needed…
  - e.g. Effort on CAPAs should be commensurate with the risks…

In this way, the principles of QRM as per ICH Q9 are emphasised

Other QRM examples…

WRT Investigation and Decision Making

- 8.13: The decisions made during and following quality defect investigations should reflect the level of risk that is presented by the quality defect
  - as well as the seriousness of any non-compliance with respect to the requirements of the marketing authorisation / product specification file, or GMP.
- 8.13: Such decisions should be timely to ensure:
  - that patient and animal safety is maintained
  - in a way that is commensurate with the level of risk that is presented by those issues

Root Cause Analysis and CAPAs

Referred to in the section on Procedures, but also:

- 8.16: An appropriate level of root cause analysis work should be applied during the investigation of quality defects.

- 8.17: Where human error is suspected or identified as the cause of a quality defect, this should be formally justified
  - Care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.

- 8.18: Appropriate corrective and/or preventative actions (CAPAs) should be identified and taken
  - The effectiveness of such actions should be monitored and assessed

Product Recalls

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Guidance better reflects risk-based recalls and their complexity

- 8.25: Consideration should be given, following consultation with the Competent Authorities, as to how far into the distribution network a recall action should extend
  - taking into account the potential risk to public or animal health
  - and any impact that the proposed recall action may have

- 8.27 It should be considered whether the proposed recall action may affect different markets in different ways
  - Appropriate market-specific risk-reducing actions should be developed and discussed with the concerned competent authorities
  - The risk of shortage of an essential product… should be considered before deciding on a risk-reducing action such as a recall

Other Risk Reducing Actions

Recalls are not the only market actions to consider…

- 8.31 In addition to recalls, there are other potential risk-reducing actions that may be considered in order to manage the risks presented by quality defects.
  - Such actions may include the issuance of cautionary communications to healthcare professionals in relation to their use of a batch that is potentially defective.
  - These should be considered on a case-by-case basis and discussed with the concerned competent authorities.

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Stakeholder Comments…

Stakeholder Comments… mid-2013

8 sets of stakeholder comments were received…

- EFPIA
- ISPE
- BPI Germany
- EIGA (European Industrial Gases Association)
- IFAH Europe (Int'l Federation for Animal Health)
- Leem (Les Enterprises du Medicament) France
- One individual company
- One private individual

All comments were reviewed - most were very detailed and constructive

Stakeholder Comments… mid-2013

- Strong general support for the draft revision
- Several editorial suggestions – renumbering sections, etc.
- Some comments that there was not enough QRM reflected in the draft, others that there was too much!
- One stakeholder opposed the requirement to classify all retrievals of products from the market, as a result of quality defects, as recall actions
- Regarding reporting of defects and recalls to CAs, suggestion that only defects and recalls in life-saving medicines should be reportable
- One stakeholder wanted a requirement that the QP be involved in all recall decision-making
- The new text allows for the rework of recalled batches – comments around the disposition of those batches

Stakeholder Comments… mid-2013

- Suggestion that the Class I, II and III system for recalls in the Compilation of Community Procedures be incorporated into Ch 8
- Suggestion that only stock retrievals from pharmacies and patients be viewed as recalls
- Suggestion to define the meaning of the term 'distribution network' in Ch 8
- Suggestion to require all defect info to be added retrospectively into batch records
- The new text moved away from having a designated person responsible for complaints and for the execution and co-ordination of recalls
  - Some opposition to this
  - The text refers to 'appropriately trained and experienced personnel'

Final thoughts

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Ch 8 has been significantly revised & modernised

- It comes into effect on March 1st, 2015
- It is hoped that its focus on QRM, Root Cause Analysis, CAPA and Decision-making will be of value
- It provides important new guidance on:
  - What is expected to be addressed in quality defect procedures
  - When is a stock retrieval to be classified as a recall action
  - Recalls and other risk-reducing actions
  - Recalls of IMPs, communication with Sponsors, etc.
  - Human error issues
  - Trending of defects
  - Reportability of defects (including unplanned deviations)