Risk-Based Quality and Safety Management in Clinical Trials with Combination Products in Global Regulatory Environment
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**Background**
Newly emerging products which combine drugs, devices, and biologics are expected to provide new opportunities in bridging device and drug capabilities and establish synergies while bringing sophisticated combination products to consumers. The emergence of these novel products has triggered new regulatory, strategic, and technological challenges. While progress has been made at clarifying the issues that arise most frequently, regulatory authorities and product developers continue to struggle with complex regulatory and technical issues encompassing the development programs for combination products. A risk-based approach requires not only a strategy but also tools to define key indicators to measure specific risks. Key risk indicators (KRIs) and risk-based quality management systems should focus on safety of research subjects and data integrity.

**Goal**
To come out with recommendations for risk-based quality, compliance, and safety management throughout the lifecycle of combination products, while these products are being tested in clinical trials in particular, in changing regulatory environment.

**Methods**
We analyzed current regulatory guidelines throughout the life cycle of combination products and compared old and new approaches to risk-based quality and compliance management for current good manufacturing practices and during preclinical and clinical phases of combination products development. Cause–effect analysis for two major risk categories in clinical trials with combination products was performed.

**Discussion**
Risk-Based Quality Management Proposed Approaches:
- Prioritization and risk mitigation approaches across several dimensions:
  - Protection of study subjects - rights and integrity, safety
  - Credibility of data and results
  - Stratified according to knowledge of investigational product

Customized approach depending on:
- Protocol complexity
- Therapeutic indication and nature of endpoints, population comorbidities, concomitant medications
- Administration of investigational product (timing of administration, dose, formulation, route)
- Complexity of study procedures and data points collection, nature of intervention
- Vulnerability of the study population

Conclusion
Combination products, due to their specific nature, can increase risks while being tested in clinical trials. Metrics critical to risks and quality management should be linked to particular processes within development program for combination products.