Risk Based Inspections In India- An Overview

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Outline

- Introduction to Risk
- Origin of RBI in India
- Concept of Risk Management
- Outcome of the RBI in 2016
- RBI-2022/23
- Summary of outcome
- Conclusion


Plan
Management
Analysis
RISK
Process
Assessment
Strategy
Control
Company

Risk Management - Concept & Origin

- Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.
- Concept of Risk Management is applied across sectors since long
- Origin in Pharma can be attributed to the US FDA Task Force on Risk Management in 1999
- The concept was freezed in US FDA document *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach*.
- It includes implementation of risk-based approaches that focus both industry and the regulator attention on critical areas

Risk Origin Contd..

- Out come is Creation of a risk-based model for inspectional oversight
- Identify and audit Areas of high risk
  - Electronic Records
  - Aseptic processing
- Paradigm Shift from rule-based compliance to risk based view of quality and compliance
- The concept has evolved to the adoption of a quality systems model for quality management and regulation

Origin of RBI in India

REPORT ON COUNTRYWIDE SURVEY FOR SPURIOUS DRUGS

Drugs Survey
NSQ and Spurious Drugs Data - Source wise*

RETAIL OUTLETS	Spurious: 0.0237%	NSQ: 3%
GOVT. SOURCES	Spurious: 0.0597%	NSQ: 10.02%
PORTS(IMPORTS)	Spurious: NIL	NSQ: NIL

National Average*

(Retail, Government Sources and Ports)

Spurious: 0.0245%	NSQ: 3.16%

*Statistical Analysis by ISI, Hyderabad

Press Information Bureau
Government of India
Ministry of Health and Family Welfare

17-April-2015 17:01 IST

Health Ministry conducts raids on Ghazipur dairies misusing oxytocin to extract milk

Reports had appeared from time to time that oxytocin injections are being illicitly used by the dairy owners to extract milk from milch animals leading to its harmful effects on humans as well as livestock.

Information was received on 13 April 2015 that the drug is being stocked and supplied illegally at Ghazipur Dairy in Delhi by certain unscrupulous persons. Surveillance was conducted by the officers of North zone of CDSCO on 14 April 2015 to collect information about the movement of the drugs and hideouts of the persons involved in the activity. After getting confirmed leads, raids were conducted on 15 April 2015 at the hideouts to catch the culprits red-handed by the five officers of North Zone of CDSCO along with four Drug Inspectors of Government of NCT, Delhi with the assistance of Police authorities of the area at two sites.

Large quantities of oxytocin injection in plastic bottles and other veterinary drugs were seized from their premises. A list of the drugs seized is as below-

Drugs seized at Site No. 1

S.No	Name of Drug	Batch No.	Quantity stocked	Manufactured by
1.	Oxytocin Injection 100ml	OXY 003	390 Bottles	M/s Priya Pharmaceuticals 823001 B.C Kanpur Lic. NO.1344199
2.	Tan Tanatan Dudh Dhara *(Suspected to be containing Oxytocin)*	Not mentioned	160 Bottles	M/s Durga Chemical, Gaya , Bihar

Genesis of RBI in India

- Media reports on the quality of drugs manufactured in the country
- Findings of survey conducted by NIB to assess the presence of spurious and substandard drugs in the country
- Investigations carried out on the misuse of Oxytocin
- In Mar.2016, DCGI constituted a team to examine the modalities and propose detailed plan of action
- It was decided to carry out risk based inspections of manufacturing premises in respect of non-compliance of GMPs and other regulatory non-compliance in the order of high, medium and low risk.


PROCESS
OBJECTIVE
SOLUTION
INDEX
EVENT
BUSINESS
TREATMENT
SCOPE
ANALYSIS
PROBABILITY
STRATEGY
IDENTIFICATION
COST
EVALUATION
RETENTION
METHOD
CONTEXT
RISK
OPPORTUNITY
RESOURCE
AVOIDANCE
PROJECT
PRIORITIZATION
SHARING
REDUCTION
KNOWLEDGE
IMPACT
MONITOR
IMPLEMENTATION
ASSESSMENT
PLAN
STANDARD
MANAGEMENT
CONTROL

Principle, Concepts & Tools of QRM

This QRM tool was designed in line with the principles, concepts and guidance set out in the following official documents:

- ICH Q9 - Quality Risk Management
- The EMA Compilations of Community Procedures Document No. INS/GMP/499073/2006 – A Model for risk-based planning for inspections of Pharmaceutical Manufacturers
- ICH Q10 – Pharmaceutical Quality Systems
- Annex 20 to the PIC/S GMP Guide

Basic concepts

Quality Risk Management (ICH Q9)

The ICH Q9 document on Quality Risk Management was adopted at step 4 at the ICH Steering Committee meeting on 9 November 2005.

Quality Risk Management can be applied not only in the manufacturing environment, but also in connection with pharmaceutical development and preparation of the quality part of marketing authorisation dossiers. The guideline applies also to the regulatory authorities in the fields of pharmaceutical assessment of the quality part of the marketing authorisation dossier, GMP inspections and the handling of suspected quality defects. Nevertheless for coherence the text was included within

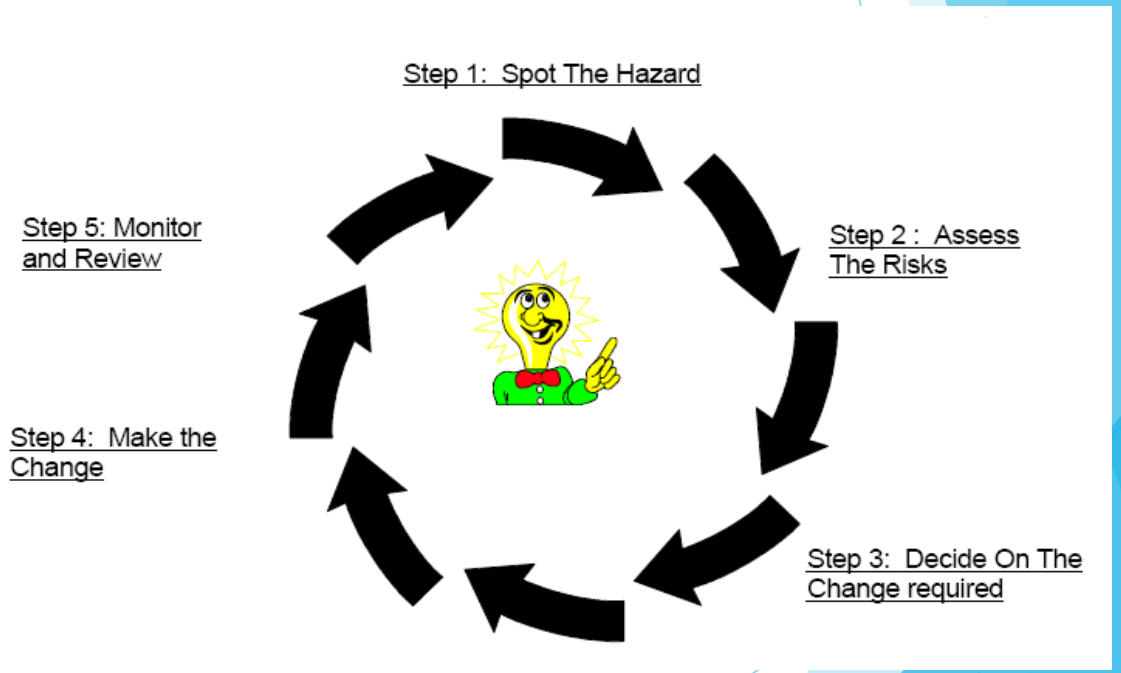
GMP Guideline, Chapter 1 (1.6) - 2009:

The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

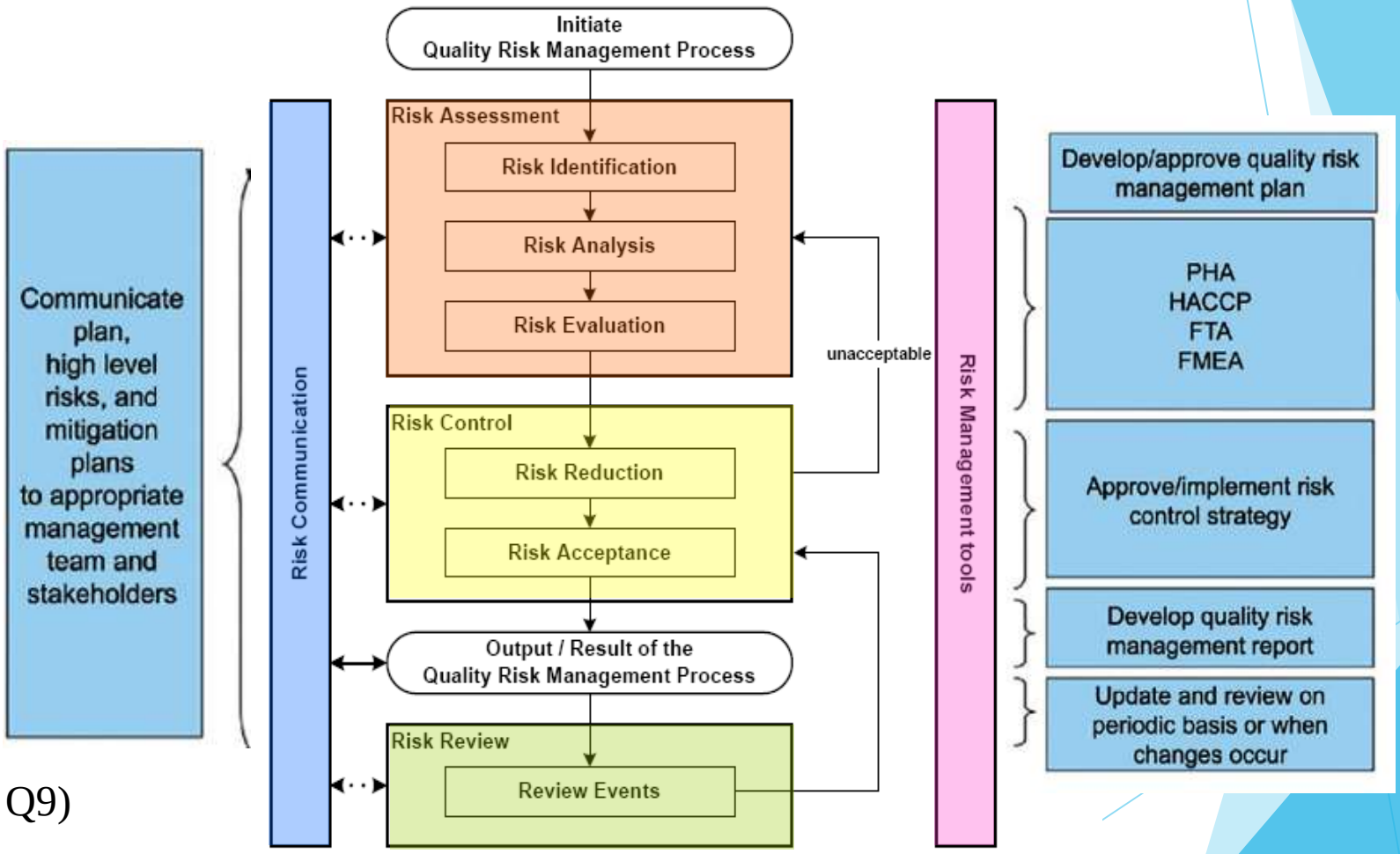
Quality Risk Management

- QRM is a systematic process
- QRM is a continuous process:



Quality Risk Management

Overview of a typical quality risk management process



(ICH Q9)

Quality Risk Assessment

- The output of a risk assessment is either a quantitative estimate of risk (numeric probability) or a qualitative description of a range of risk (i.e. high / medium / low).
- The estimate of risk may be related to a risk matrix.
- The scoring system for mitigating actions is subjective and the rationale for score categorization should be defined in as much detail as possible.

Quality Risk Control

- Risk control includes decision making to reduce and / or accept the risk within specified levels.
- Risk control should continue throughout the lifecycle of the process.
- The purpose is to reduce the risk to an acceptable level. Acceptance limits should be based upon scientific knowledge of the process.
- If the risk is acceptable, the process may remain as designed. In different cases, additional actions or controls are needed to reduce the risk.

Quality Risk Control

- Some questions can help this step:
  - Is the risk above an acceptable level?
  - What can be done to reduce or eliminate risks?
  - What is the appropriate balance among benefits, risks and resources?
  - Are new risks introduced as a result of the identified risks being controlled?

ZERO RISK IS NEVER POSSIBLE!

WHO stand

- WHO in its guidance on ‘Good Regulatory practices’ to National Medicine Regulatory Authorities stated as under:

“Inspection and enforcement efforts should be based on risk analysis and on targeted approaches. **It is impossible to inspect and take enforcement action in all cases,** so prioritization and rationalization based on assessments of risk to public health should be applied”

Risk based goals of GMP

- Ensure that resources are used effectively and efficiently to address the most significant public health risks.
- Risk in the context of pharmaceutical quality : Depends on the potential harm associated with the loss of pharmaceutical quality

Needs and Expectations of Patients

For drug quality, what are the needs/expectations of patients?

- Clinical performance or efficacy
  - Drug performs as described in the approved labeling
- Availability

Clinical performance attributes

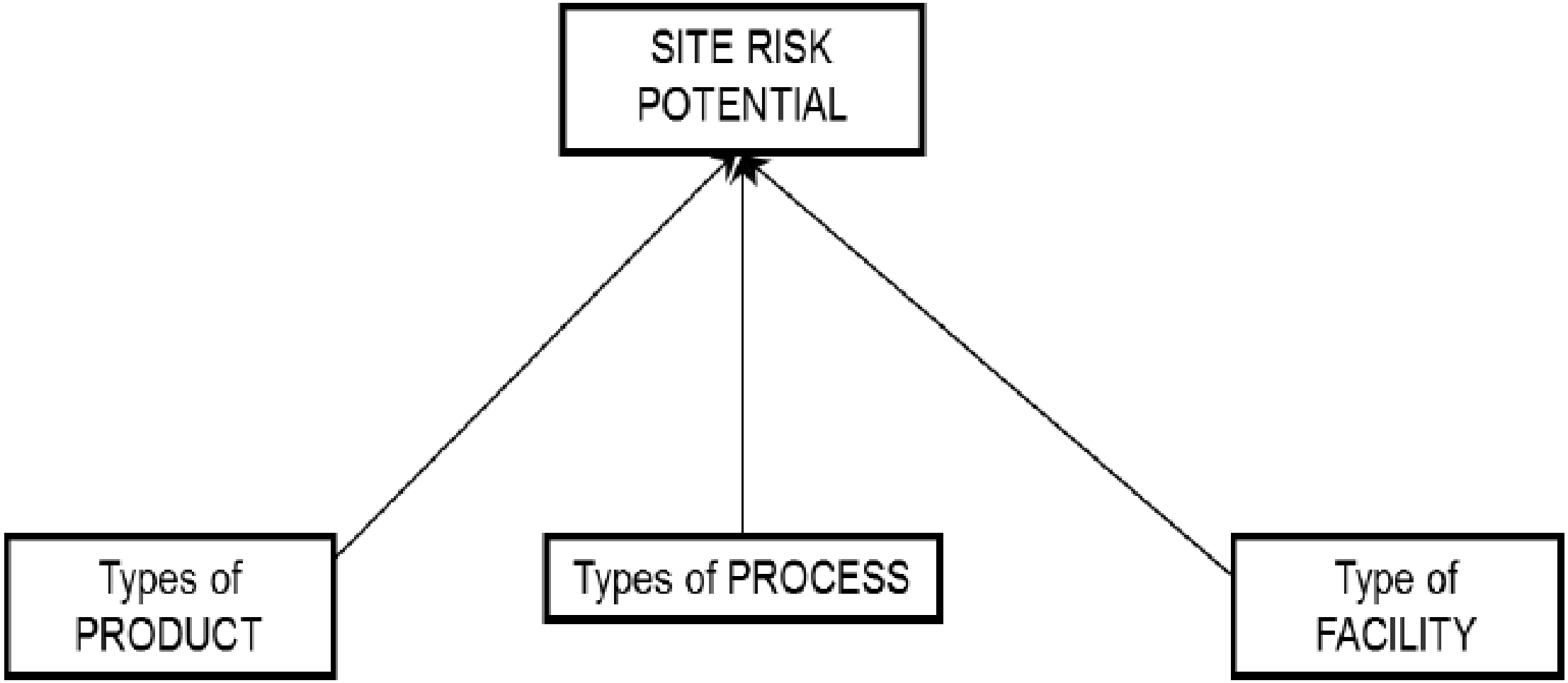
A product's clinical performance attributes are its established quality attributes, including:

- Identity/potency
- Purity
- Strength
- Bioavailability/delivery (e.g., dissolution)
- Labeling/packaging
- Physical performance/appearance (including aspects that influence adherence and acceptability)

Identify Predicted/Known Hazards to Quality Attributes: Risk Factors

- Risks to pharmaceutical quality can be identified based on the **probability** and **severity** of adverse impact on these quality attributes
- Explicitly include factors that mitigate probability/severity of adverse effects or factors that have a positive impact
- The ability to **detect** a drug product with compromised quality attributes would reduce the probability of harm

Risk-Based framework for prioritizing sites for GMP inspection



Risk Ranking Model: Product Factors

- What are the intrinsic properties of products such that deficiencies in quality, if any, would have more adverse public health impact than others?
  - sterile
  - Rx
- NSQ data identifies products or dosage forms associated with frequent and/or serious Quality failure

System based inspection approach

1. ***Quality System***
2. Facilities and Equipment System
3. Materials System
4. Production System
5. Packaging and Labeling System
6. Laboratory Control System

Why a ‘Systems’ Approach?

- Reinforces proactive compliance & reduces reliance on regulator as QA
- Extrapolation: judgment made on all products based on Systems & products actually inspected
- Potentially decreased time to inspect, overall

How is a system covered?

- Sufficiently detailed, with specific examples to determine state of control for every profile class
  - profile class = categorization of different processing conditions & product types
  - related to requirements (CGMPs)
- If System is in control, all profiles covered by system are deemed in control
- Unique profile class material/process under a system selected at discretion of Investigator

System approach

- Quality
  - Quality unit, Investigations, training, quality complaints, APR
- Laboratory
  - Stability, testing, Methods
- Process
  - PV, Process Controls, Sterility assurance
- Equipment
  - Cleaning/maintenance, calibration, design

QRM Tool

MHRA RISK INTELLIGENCE IT SYSTEM VISION

accenture ORACLE

INDUSTRY STAKEHOLDERS

Drug Safety, Research & Development, Regulatory Affairs, etc...

Data Inputs (e.g. Self-Assessment)

Manufacturing/ Other Sites

SOURCES

Regulatory Data Inputs

Data from GxP Inspections Process

MHRA INSPECTORATE

Evidence-based inputs

Qualified Market Intelligence

Media/News Sources

Whistleblower Communications

OTHER STAKEHOLDERS

Other Regulators/ Government Bodies

Aggregation of Data from across cross-domain Agency Regulatory Functions populating Risk Intelligence database at the MHRA

MHRA DATA SOURCES

Drug Safety | Licensing | Finance | *Other*

Clinical Trials | Investigations

Core "Sentinel" System Repositories

Process Licensing

Inspections

Other Inputs

Risk Bureau

Data Points represent "Risk Events"

MHRA

accenture

MHRA RISK MANAGERS

Pro-active assessment and IT-assisted capture of information from wide group of external data sources to extend baseline data –set and populate database

End-to-End Custom Application Suite for Visualisation and Management of Risk and control of Agency inspections scheduling processes

1. Collate:

Collation of Structured Risk Event Data Points in Datamart Component

2. Process:

Processing of data against RBI algorithm component identifying statistical Risk probability at Group, Company, Site, Entity and GxP-Levels

3. Business Rules:

Automated application of Business Rules to derive Suggestion of GxP Inspection Dates based on Risk Scores

4. Outcomes:

Agency Review of Inspection Dates and associated scheduling of future Inspection activity based on outcomes

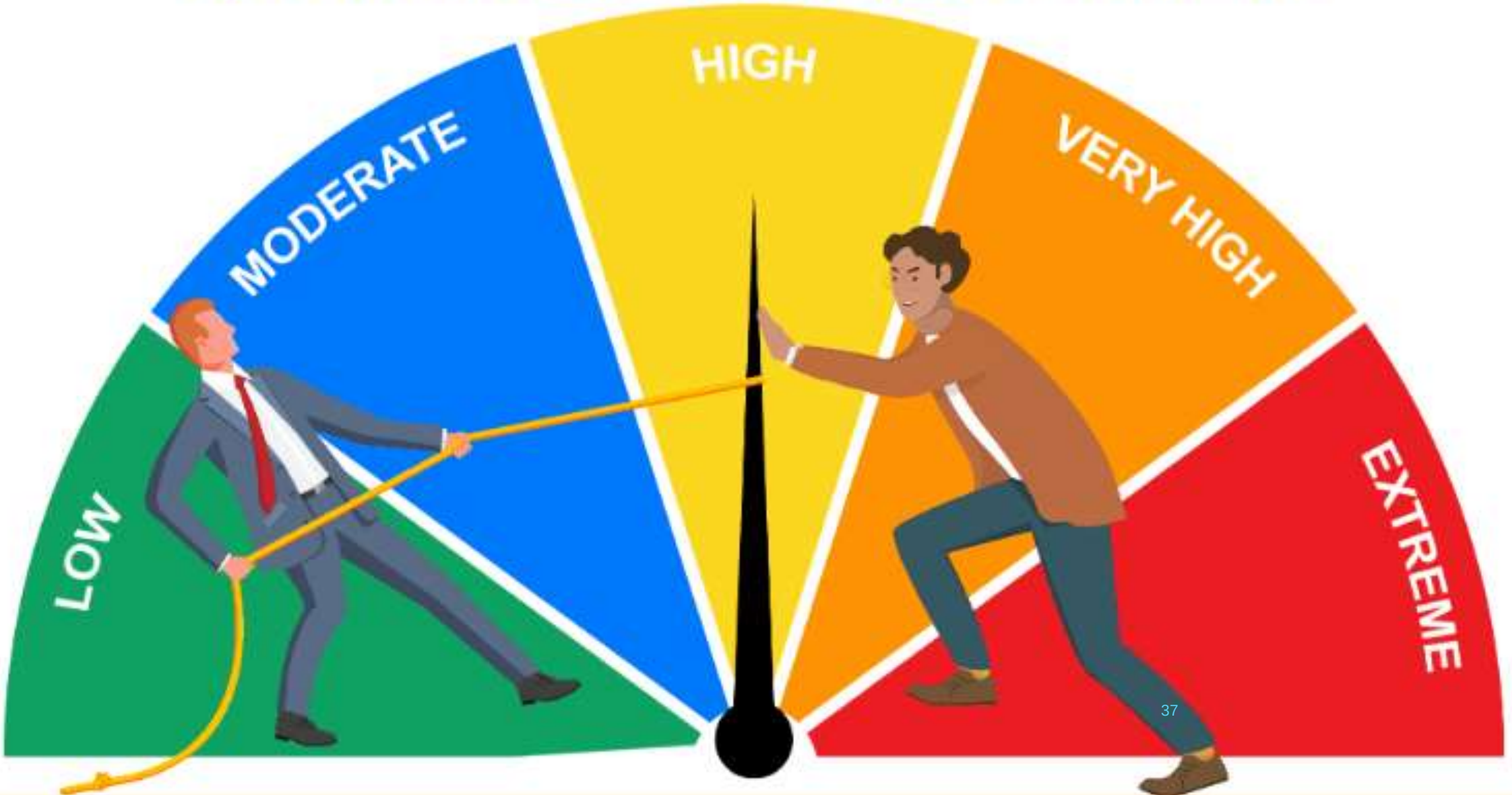
Lead to...

RISK-BASED INSPECTIONS SCHEDULE

5. Manage:

Visualisation and Tracking of Trends and Events for ongoing Risk-Based Business Process Management

QUALITY RISK MANAGEMENT



Risk based model in India

- Need of Risk based approach in India
  - Federal structure
  - Complexity of the products
  - Shortage of Inspectors
  - Uniformity of implementation
  - Quality complaints-domestic and international
- Identifying the sites posing high risk

Identification of sites

Taken into account information on NSQ drugs from the following sources to identify the sites with highest risk---

- National survey conducted by NIB.
- Reports from the laboratories under CDSCO.
- Reports from the State laboratories.
- Reports from international regulatory agencies.
- Information gathered through intelligence
- All the 130 Oxytocin injection manufacturers

List of drugs	No. of sites with 2 or more failures	No. of sites with 3 or more failures and spurious	No. of sites with 5 or more failures and spurious
CDSCO Labs & Ntl. Survey	84	43	20
State Labs	165	119	56
Intl. Quality Complaints	44	27	15
Oxytocin mfrs	130	130	9
Total	423	319	100

Recommendations

- A checklist has been prepared with risk rating the observations
- Initiate RBI at sites >5 NSQs/International Complaints and all Oxytocin manufacturers
- Inspection teams constituted with one DI each from CDSCO & State.
- Consider deputing ADC/ADI & Analyst depending on their availability
- Sites name is informed after the team reached the place
- Ins. report has to be sent immediately after completion through mail
- Orientation program for the teams
- critical parameters are identified and communicated to all the inspectors for uniform reporting
- Letter addressed to all the SDCs

Previous RBI 2016

- Identifying high risk facilities based on predefined criteria.
- Training of Inspectors of Central and State Governments including experts from Govt. testing laboratories.
- Common checklist and benchmark is laid down for uniformity.
- Inspection teams were constituted facility wise.
- Pre-notification of inspection dates to manufacturers.
- Inspection report with observations were shared with manufactures to be compliant.

2016 RBI contd..

- The classification of the findings is provided separately i.e., a comprehensive list of critical and deficient findings is tabulated in order to assign rating for the observations of the drugs inspector.

RBI system

Objectives of new system:

- To improve the quality of medicines on the market
- To improve compliance through self regulation
- To change company behaviours
- To reduce regulatory burden whilst maintaining regulatory compliance
- To optimise the use of inspection resource

Challenges faced in 2016

- Concerns of lack of legal provisions for RBI jointly with the CDSCO
- Both by the Industry and the regulators
- Lack of follow up action on the observations
- Drugs Rules were amended on 27.10.2017 to include--
- **Rule 73 AB (2)--**The premises licensed under sub-rule (1) shall be inspected jointly by Inspector appointed by the Central Government and State Government to verify the compliance with the conditions of licence and the provisions of the Act and these rules not less than once in three years or as needed as per risk based approach.

Centre Starts Probe After WHO Claims Indian Cough Syrups Behind 66 Deaths In The Gambia

WHO had highlighted that a significant contributing factor to the deaths was suspected to be the use of medicines that may have been contaminated with Diethylene Glycol/Ethylene Glycol, and said its presence had been confirmed in some of the samples it tested.

Healthcare & Pharmaceuticals | Drug & Device Trials | Regulatory | Climate Change

U.S. FDA says India-made eye drop linked to some infections, blindness and one death

Reuters

February 3, 2023 11:54 PM GMT+5:30 · Updated 8 months ago

Details of RBI carried out

Sr. No.	Phase	Number of Inspections
1	Phase-1	78
2	Phase-2	47
3	Phase-3	51
4	Phase-4	51
5	Public Testing Labs	~70
	Total	>300

Regulatory Expectations

- Compliance labelling claim
- Efficacy similar to the reference product
- Patient Safety
- Data to support the claims
- Consistency of the quality
- Quality Systems
- Regulatory compliance
- Others

Common observations during RBI

- Food supplements manufactured in the same premises
- Lack of facilities for the products licensed
- Lack of measures to prevent cross-contamination
- HVAC system absent or not adequate or not working
- Water system not validated
- Raw materials and finished goods not tested
- Poor microbiology lab facilities
- Analytical method not validated
- Lack of consistent batch size
- Lack of R & D/Poor product understanding during formulation

Common observations during RBI-2

- Lack of dedicated section for potent products
- Parenteral products
  - Hold time study
  - Media fill
  - Failing in sterility
- Issues of Data integrity
- No root cause analysis
- Lack of vendor qualification
- Lack of SOPs or failure to follow SOP
- Lack of freedom to the Technical Staff

A CAPA WITHOUT ROOT CAUSE ANALYSIS

Issues to be addressed

- Multi product manufacturing facility
- Batches not produced regularly
- Bioavailability/bioequivalence studies
- Concept of formulation development
- Quality Culture at all levels
- Continuous training
- Data integrity
- Vendor Validation

- **Management responsibility is essential** to establish and maintain a *company commitment to Quality Policy* and for the performance of the Pharmaceutical Quality System.

- Senior Management should commit formally to follow the Quality Policy
- Quality should be the responsibility of ALL involving field staff to senior / upper management
- *Responsibilities that should NOT be delegated*

Outcomes of the RBI -2022/23

- Ultimate objective is to improve the quality of drugs produced in the country
- Convergence of thoughts of the Central & the State Regulators
- Regulators know the ground reality
- Revision of Schedule-M
- Sensitization of the manufacturers through outreach programs
- Stress on digitalization
- Capacity building
- Frequent interactions among the State and CDSCO regulators
- Regulatory Accountability

Thanks

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