VISUAL INSPECTIONS OF STERILE PRODUCTS

IPA QUALITY FORUM SUBGROUPS 2020-21
SUB GROUP 4

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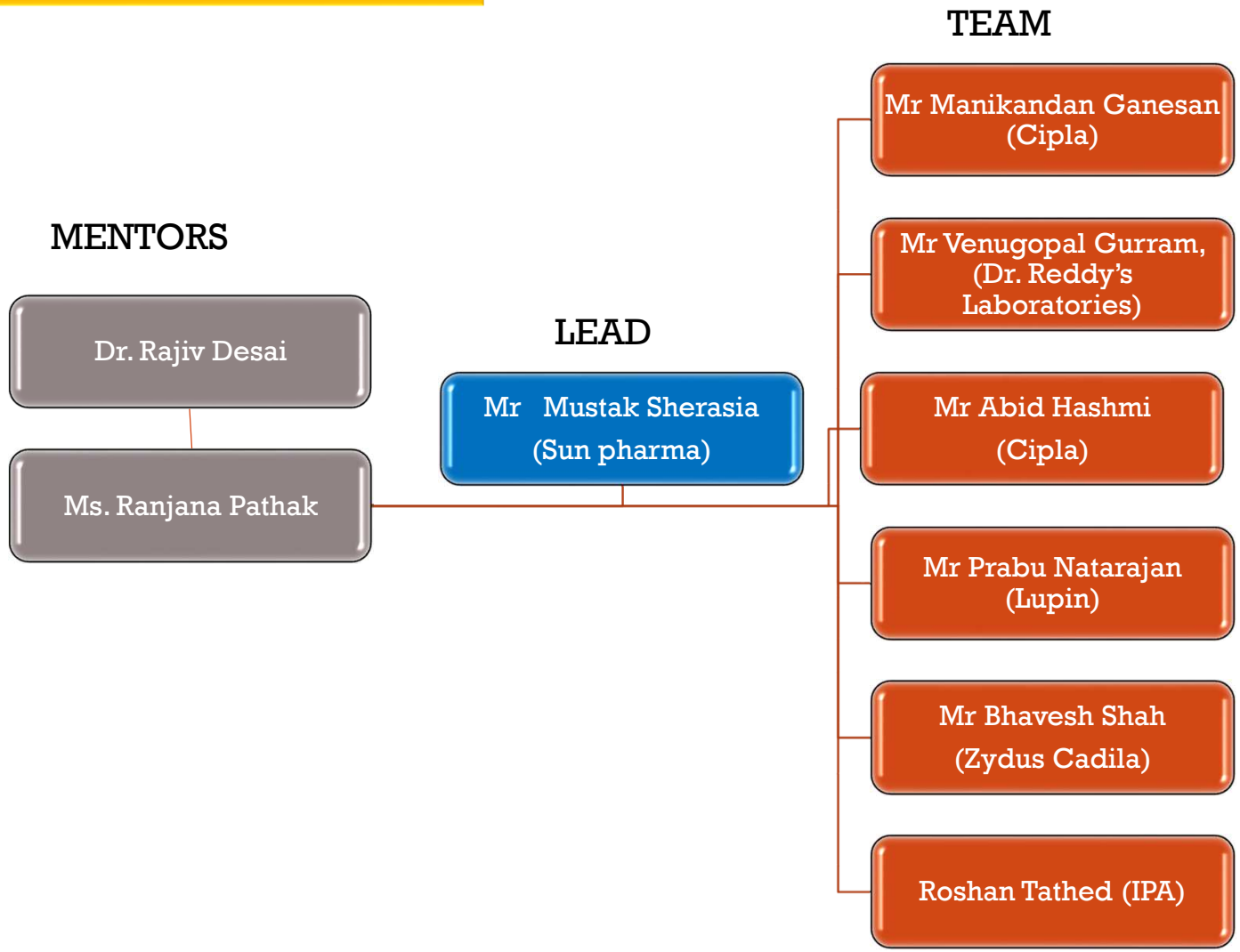
TEAM INTRODUCTION



1. PREFACE

In 2020-21, the QF focused on one of the key priority areas: Visual Inspection of Injections for Visible Particles. It took upon itself the challenge of establishing robust and seamless visual inspection and process, and release a comprehensive set of guidelines in 2021.
The QF reflects the long-term commitment made by the IPA to address key issues facing the industry and develop a series of best practices."

2. INTRODUCTION

Purpose and Scope

- Applicable for the visual inspection activities carried out for different sterile dosage forms, i.e., injectable, ophthalmic products, lyophilized products, suspensions, and media fill containers.

Background

Inspection Process Capability

- Zero defects
- 100% inspection
- detection is a cumulative function of visible attributes

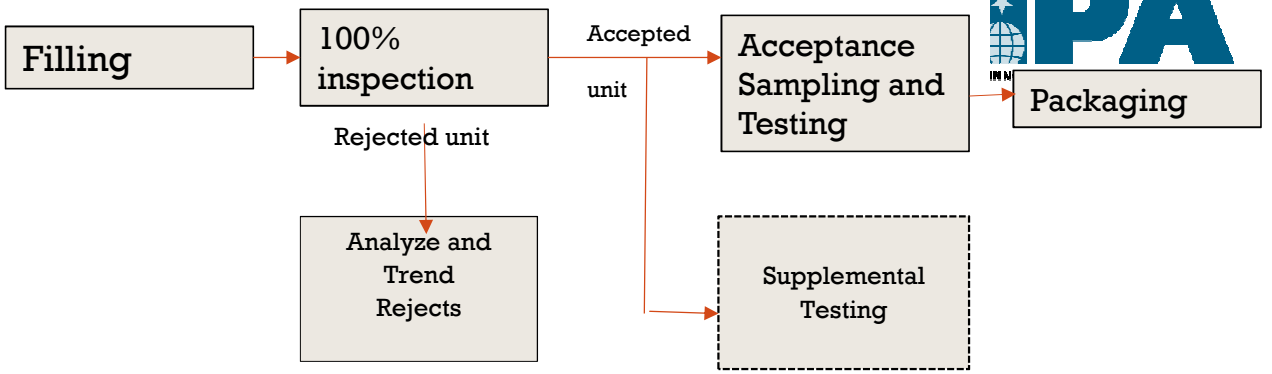
Patient Risk

safety considerations related to particulate matter in injections must be assessed for each drug product, intended patient population, and method of administration

3. Inspection Process Flow

Inspection Process Flow

100% Inspection



AQL Sampling and Testing

ANSI/ASQ Z1.4, ISO 2859, JIS Z9015

Defect Category	AQL Range (%)
Critical	0.010–0.10
Major	0.10–0.65
Minor	1.0–4.0

Remediation and Alternative Practices

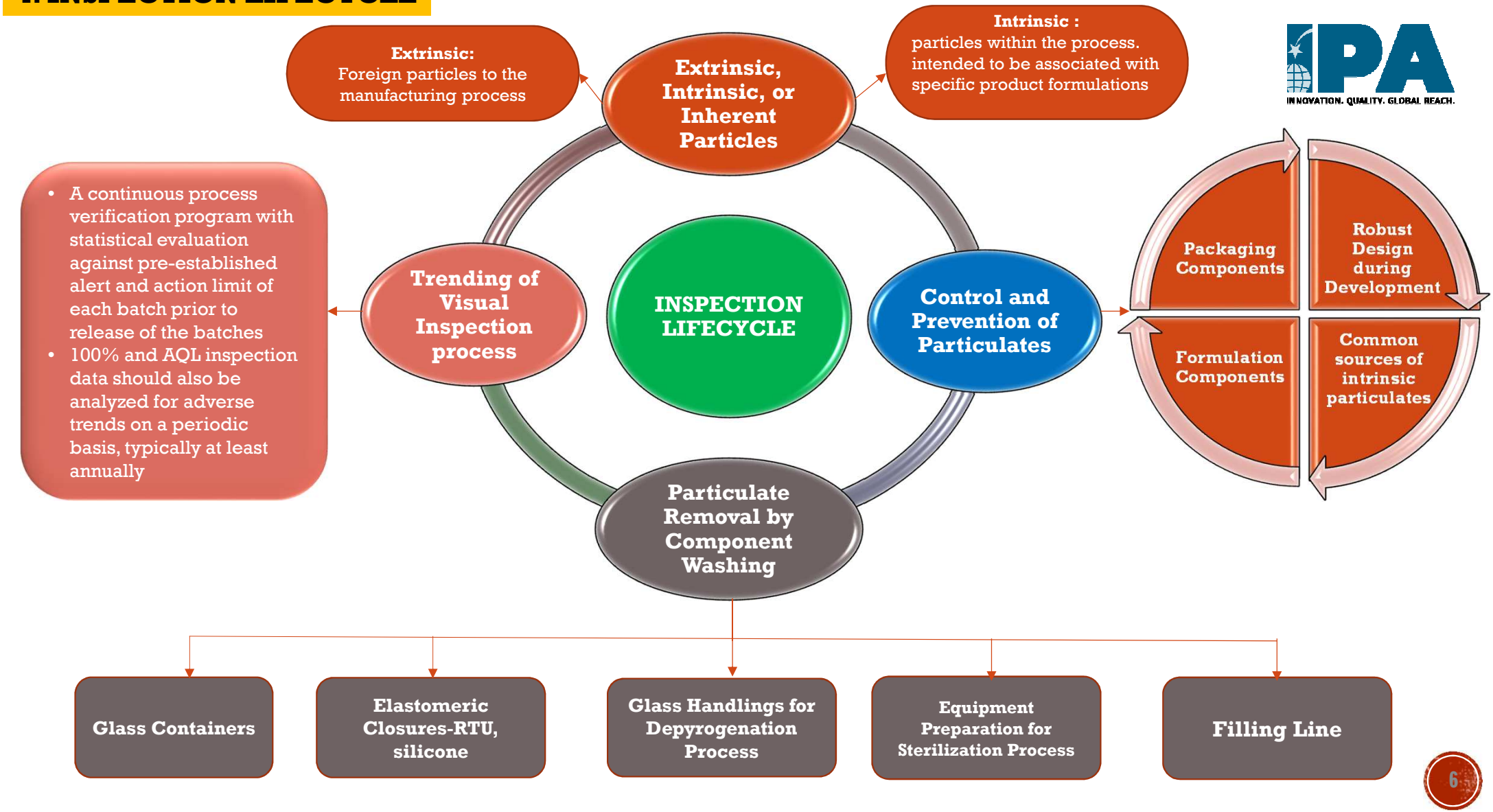
REINSPECTION

repeating the 100% inspection followed by acceptance sampling inspection if the initial 100% inspection is not successful

TWO-STAGE INSPECTION

In cases where an assignable cause, such as formation of air bubbles or specific container or closure variation, results in a high false-rejection rate (rejection of acceptable units), the use of a second inspection step may be considered

4. INSPECTION LIFECYCLE



5. Interpretation of Visual Inspection Results

Defect Classification

- **Critical Defects:** Serious adverse reaction or death of the patient
- **Major defects:** Defect causes impairment to the use of the product
- **Minor defects:** No Impact, cosmetic in nature, affecting only product appearance or pharmaceutical elegance

Unique Products and Containers Considerations

- Lyophilized Product
- Powder Product
- Emulsion and Suspension Product
- Amber Containers
- Translucent Plastic Containers
- Large Volume Containers
- Combination Products

Alternate Inspection Strategies for Supplemental Testing

- Transfer
- Filtration
- Clarification.
- Sieving

6. Inspection Methods and Technologies

Manual Visual Inspection (MVI)

- viewing filled and sealed containers under controlled conditions.
- The quality decision, to either accept or reject the container, is made by a trained person

Critical Process Parameters

Light intensity	• Light levels NLT of 2,000 – 3,750 lux • light levels as high as 10,000 lux for amber glass
Background and contrast	• Increased contrast improves detection • white/black backgrounds provides good contrast.
Inspection rate	• 10 second per container • 5 second each against both black and white backgrounds
Container handling and movement	• careful swirl or inversion of the liquid product within the container
Magnification	• magnification can be helpful for critical examination of a small number of units

Inspector Fatigue and Ergonomic Considerations

It is recommended that inspectors be given a break from performing inspection at least every hour. This break should allow time to rest the eyes and mind, and may be achieved with a short rest (e.g., 10 min/hour) or a longer meal break.

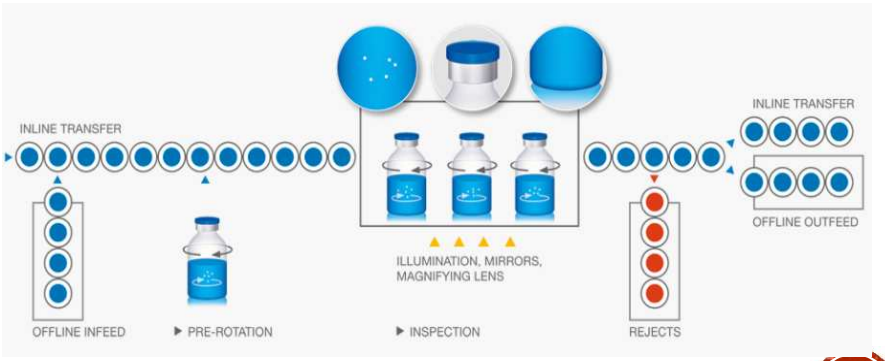
6. Inspection Methods and Technologies

Semi Automatic Visual Inspection (SAVI)

Semi-automated visual inspection combines automated material handling of the containers to be inspected with human vision and judgment to make the decision to accept or reject.

Critical Process Parameters

Light intensity	• Light levels NLT of 2,000 – 3,750 lux • light levels as high as 10,000 lux for amber glass
Spin speed	• **rotation rate of containers** to ensure full rotation of vials in the inspection zone
Inspection rate	• controlled by the speed of the infeed conveyor/rollers to produce an acceptable detection rate for defects of interest



The contrast of foreign particle is intensively enhanced under the strong light beam and the container can be inspected very quickly.

6. Inspection Methods and Technologies

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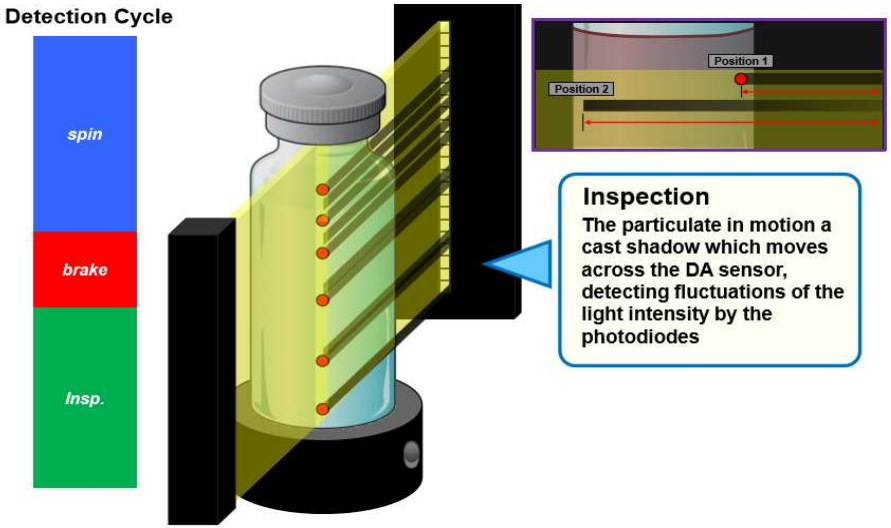
Automated Visual Inspection (AVI)

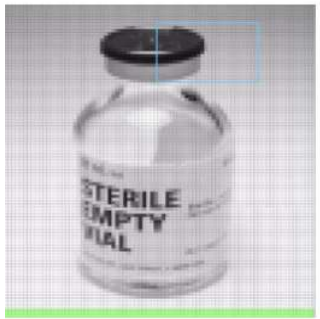
Automated Visual Inspection (AVI) machine acquires a sequences of images of product appearance by electronic sensing, processes them according to parameter setting of recipe (pre-programmed acceptance criteria), and provides inspected results as 'accepted' or 'rejected' automatically

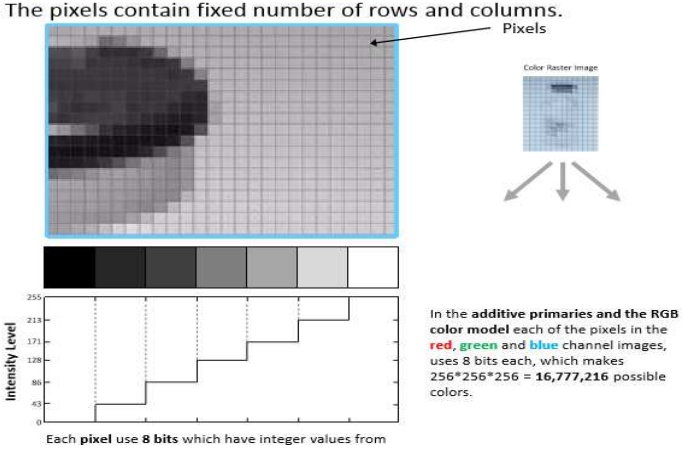
Light Obscuration Methods (static division detection)



Imaging Methods (camera inspection detection)

The digital raster images acquired by the digital camera have a finite set of pixels which are the smallest individual element in an image, holding quantized values that represent the brightness of a given color at any specific point. The pixels contain fixed number of rows and columns.





6 X-RAY MACHINE FOR POWDER AND LYOPHILIZED PRODUCT

Focus detection for Glass ,metallic and rubber particles in Powder and Lyophilized Product

7 PREPARATION AND MAINTAINANCE OF CHALLENGE KIT FOR QUALIFICATION

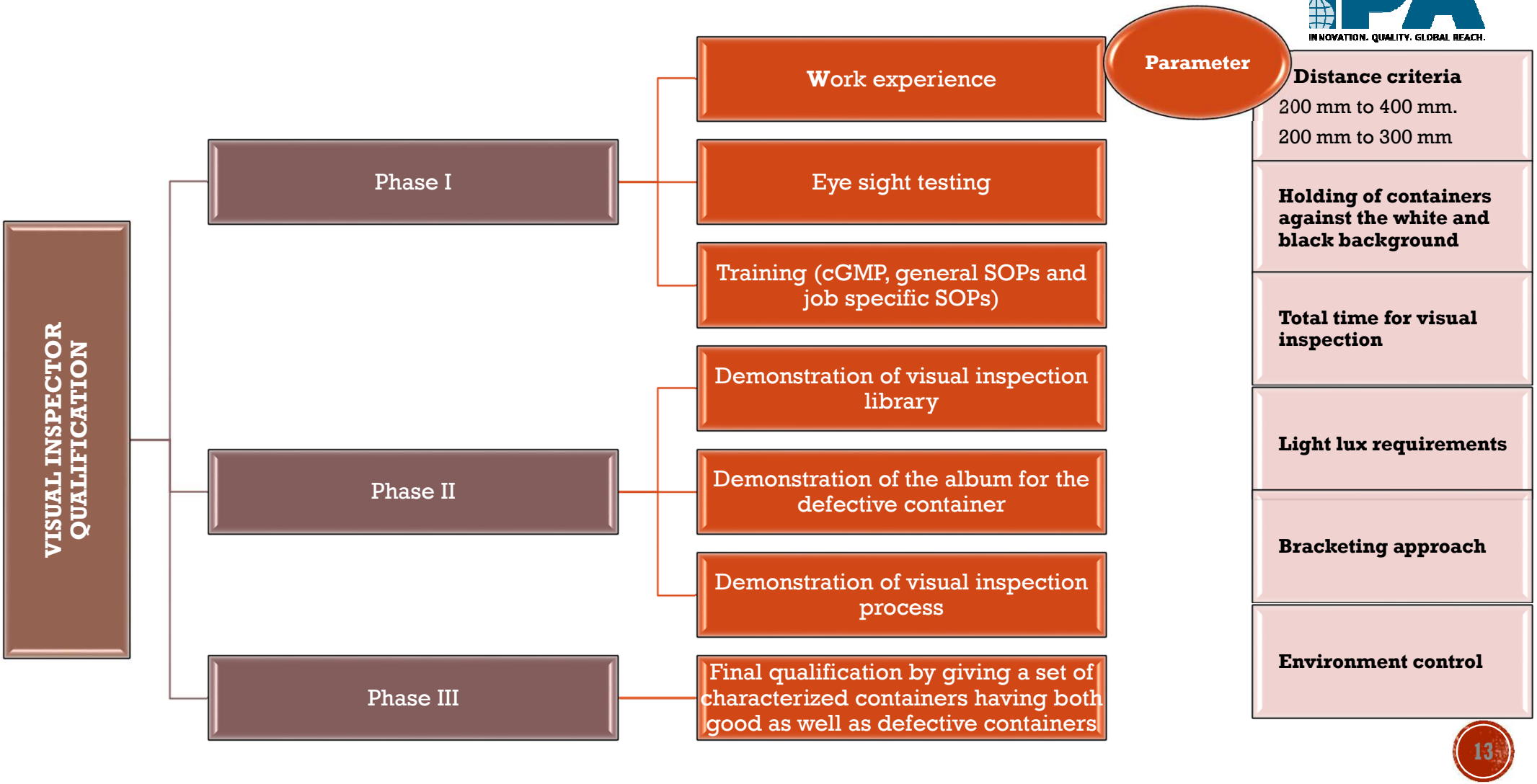
PREPARATION

- Kit creation under controlled environment.
- select naturally occurring particulates and physical or cosmetic production rejects removed from product lots.
- Containers must be absolutely free of visible particles. One container must have only one defect.
- Defined expiry date based on shelf life of product.
- Good samples and rejection from routine batch
- One rejection for each category available
- maximum number of containers which can be inspected in one hour.
- Defect distribution from 5% to 15%, including critical, major and minor defects
- Particles size used for standard rejected containers should be between 100 µm to 250 µm (500 – 2,000 µm for fibers).

MAINTAINANCE

- Establish procedures for maintenance, issuance, retrieval and periodic replacement of the visual inspection kit.
- A master list of the qualification kit with details of defective/good container and respective allotted numbers should be prepared and approved.
- The constructed used for initially qualification & periodically for requalification.
- storage under controlled secured conditions with identification label.
- If container in qualified kit being impaired with defect of container-closure or content, it shall be replaced with pre-qualified back-up containers.
- If there is gross physical damages as well as changes in content of containers in kit, the kit shall be discarded.
- A documented procedure shall be followed for the disposal of such kit and shall be pre-approved by Quality unit at site.

8 VISUAL INSPECTOR QUALIFICATION



9. VISUAL INSPECTION OF MEDIAFILL CONTAINERS

Inspection performed by Qualified inspector same as product. Focus on turbid container

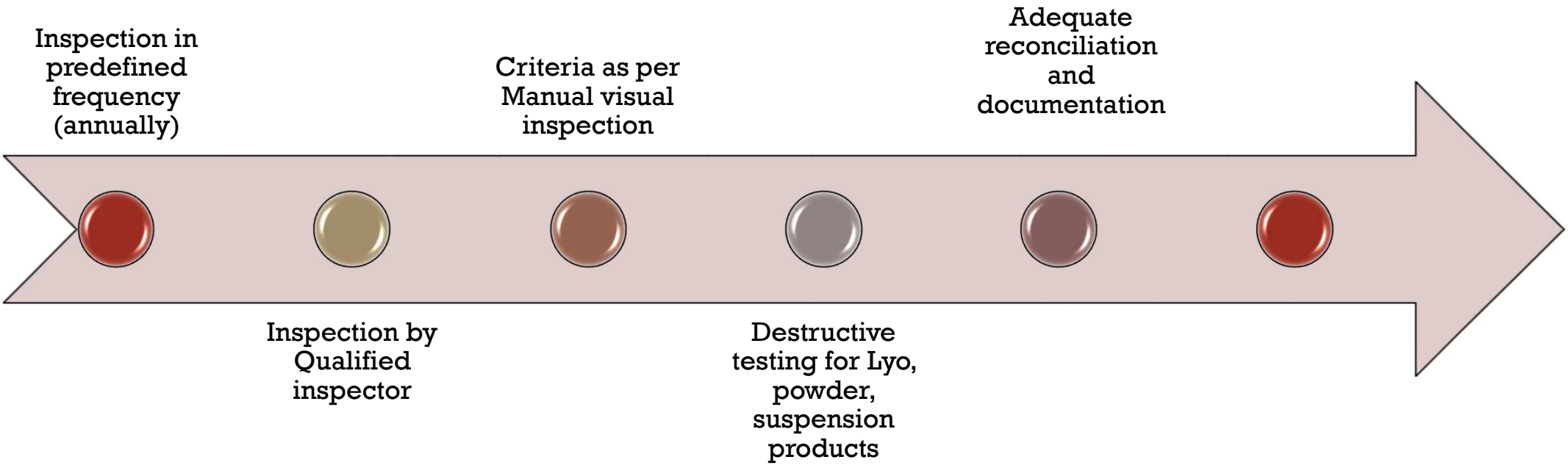
Visual inspection Kit and media fill library preserved from previous mediafill/Trial Run

Expiry periods for good container defined based on risk assessment

Utilize Color Indicating media Powder for Media fills to easily defects contaminant by change in color medium

Qualification should be carried out with a quantity of physical rejection, containers inoculated with microorganisms

10. Inspection of Retain/Control Samples



11. Investigation Considerations for Visible particles

- **Evaluation of following parameters is recommended to considered for Investigation of higher Visual inspection rejection :**
  - Personnel training and qualification
  - Inspection booth/machine qualification/performance
  - Inspection process
  - Rejection pattern, e.g., entire lot or portion of lot
  - Type of defects
  - Type of dosage form
  - Raw materials assessment
  - Packing material assessment
  - Manufacturing process assessment (compounding to final stage of process)
  - Products rejection trends
  - Filling line rejection trends
  - Breakdown history of filling line
  - Preventive maintenance of filling line
  - Environment controls
  - Supplement testing
  - Over all rejection trends
  - Identification of defects (morphology, IR, SEM, X-Ray analysis and elemental analysis)
  - Source of defects
  - Vendor assessment
  - Risk assessment for visual defects
  - HHE evaluation for visual defects
  - Root cause analysis
  - Corrective actions
  - Preventive actions

THANK YOU