International Procurement and supply Schemes Part II

by Dr. Nora Dellepiane

Workshop: Global Registration and Vaccine Shortage

Taipei, Taiwan 6 to 10 March 2017

Quality & Regulation Biologics

Outline of the presentation

Vaccine Supply Mechanisms

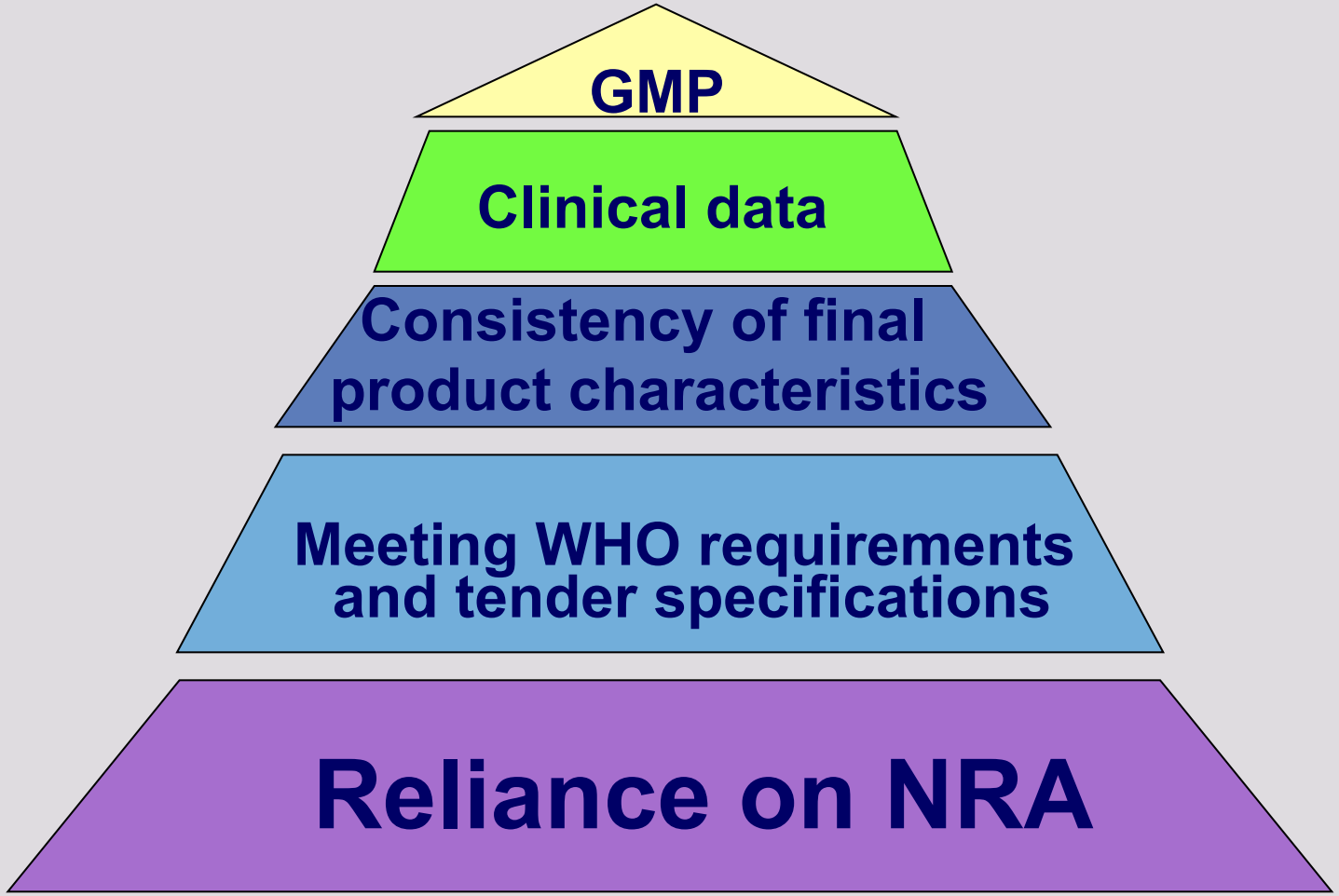
Ensuring quality and safety of products for purchase

WHO prequalification

- Site audit
- Collaboration with NRA in producing country
- Post- PQ monitoring

Quality & Regulation Biologics

Prequalification of vaccines: Principles



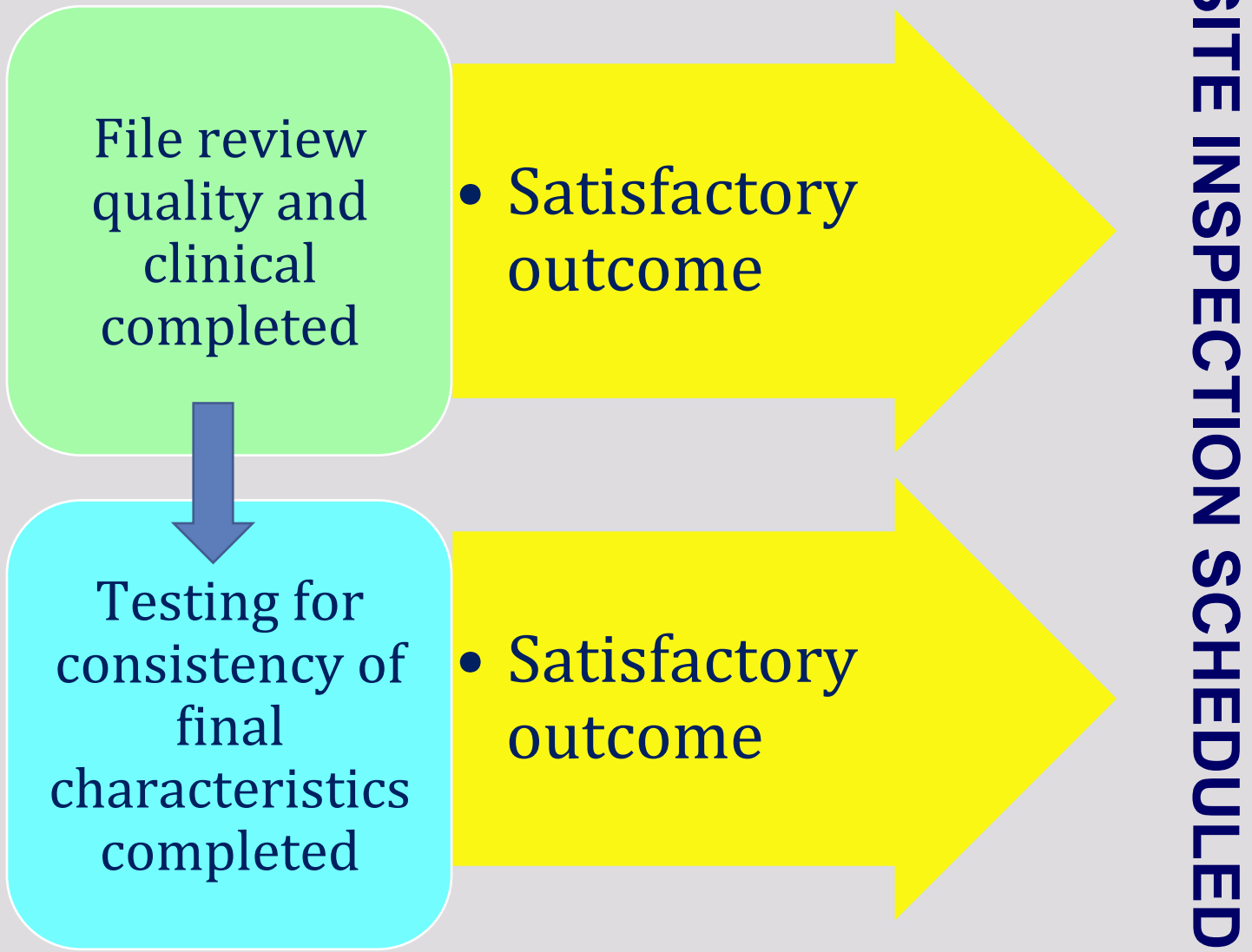
Quality & Regulation Biologics

PREQUALIFICATION STEPS

1. Scientific review of dossier (PSF or CTD)
   - Quality part
   - Clinical part
2. Testing of samples
3. **Consultation with responsible NRA**
4. **Product related site inspection of the manufacturer**

http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html

Timing for site inspection



We have discussed meaning of GMP

World Health Organization defines GMP as:

"that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization"

Quality & Regulation Biologics

We have discussed meaning of QMS

What is a quality management system?

According to WHO, quality management is usually defined as the aspect of management function that determines and implements the "quality policy", i.e. the overall intention and direction of an organization regarding quality, as expressed and authorized by top management. The basic elements of quality management are:

- Appropriate infrastructure encompassing the organizational structure, procedures, processes and resources
- Systematic actions to ensure adequate confidence that a product (or service) will satisfy the given requirements for quality. The totality of these actions is termed "quality assurance"

- TRS 908, Annex 4; 2003

Quality &
Regulation
Biologics

.... And also QA

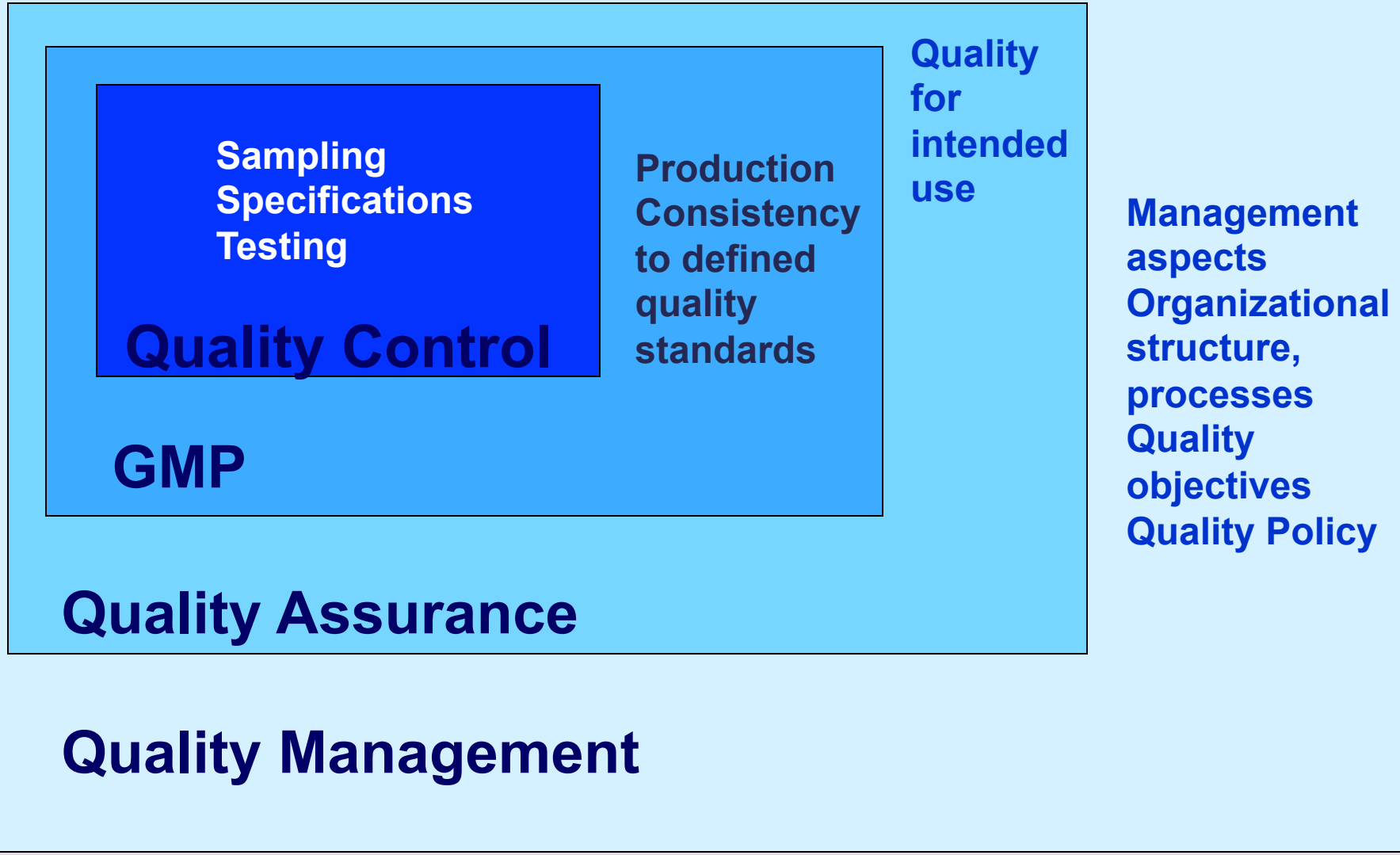
What is Quality Assurance?

Quality Assurance is a wide ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use.

TRS 908, Annex 4; 2003

Quality & Regulation Biologics

Quality Relationships



Objectives of the site inspection

To verify that

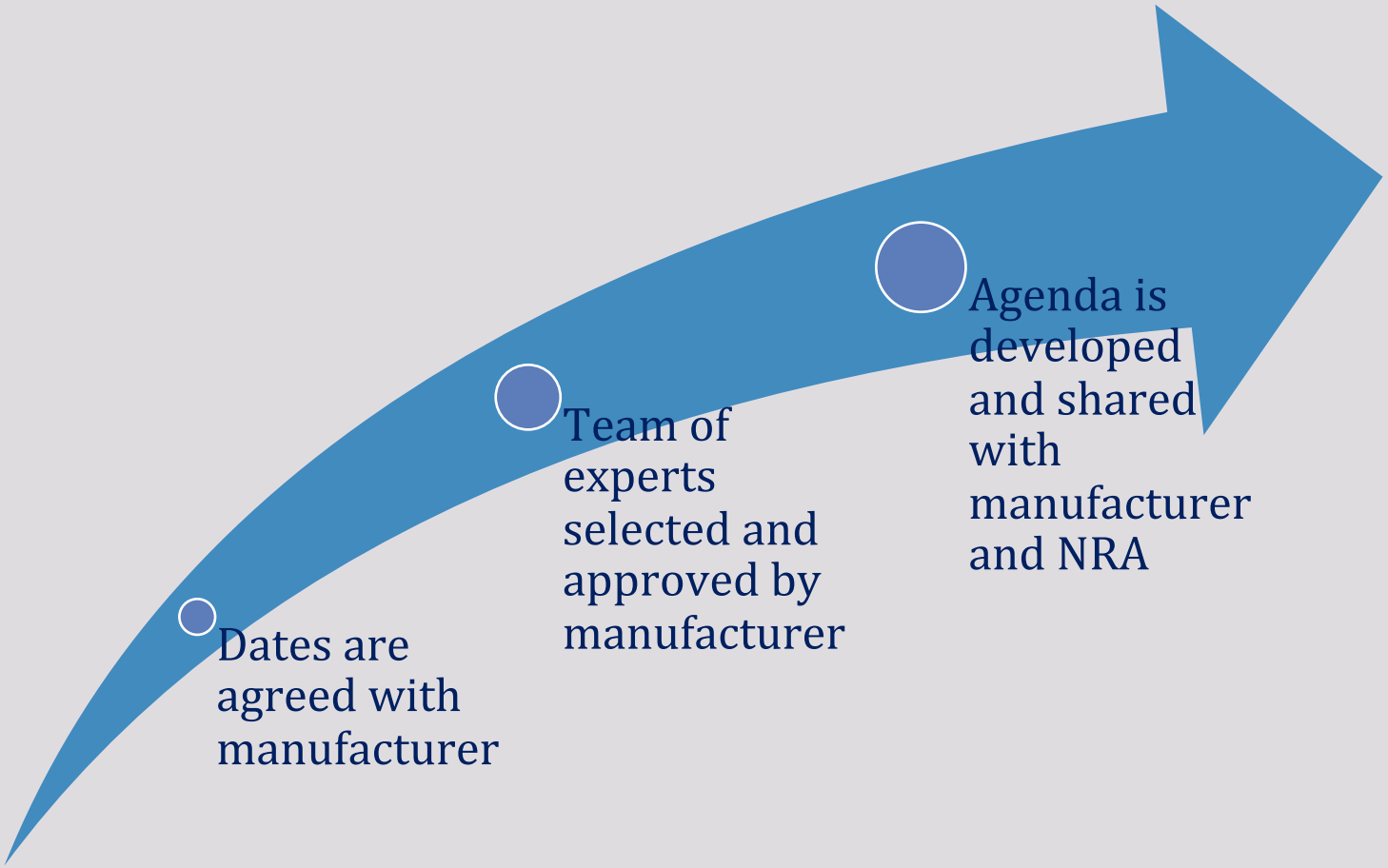
Product is produced in accordance to WHO GMP recommended requirements, QA in place and QMS is implemented

Product meets the WHO recommended requirements for quality, safety and efficacy (TRS documents)

Product meets the specifications of the UN tenders

Quality & Regulation Biologics

Planning the inspection



Quality & Regulation Biologics

Planning the inspection: team

Product expert

QC expert

GMP expert

Team leader WHO staff

In some cases translators may be needed

Quality & Regulation Biologics

If more than one product will be reviewed additional experts will be proposed according to needs

Planning the inspection: team

- Experts are proposed and asked to fill Declaration of Interest form.
- If no particular interest is identified manufacturer's agreement is requested.
- If a conflict of interest is identified, manufacturer is requested to review and advise

NOTE: The NRA of the producing country is requested to participate of the inspection to the manufacturing facilities, and their representatives are invited as observers

Quality & Regulation Biologics

Planning the inspection: agenda

- An agenda is developed describing activities on a daily basis which is sent to the manufacturer and the NRA for information
- NRA representatives are requested to join the auditors as observers
- Production is expected to be running at the time of the audit and some steps of the process may be observed by one or more team members
- Some QC tests may be observed by expert/s in QC
- The team requires availability of a room to discuss in private and prepare the draft report. Projecting and printing facilities are required
- The team provides feedback to staff audited on ongoing basis and also at the end of each day
- A formal debriefing session for management is organized on the last day

Quality & Regulation Biologics

3. Consultation with NRA

WHO team meets NRA of country of origin to:

- discuss ongoing regulatory oversight of the product
- Review data available with the NRA (outcome of GMP inspections, test results, PMS data, etc)
- Agree on collaboration for exchange of information about performance of the product in the field and any quality or GMP issues that may come up
- Information exchange is both ways
- An agreement for such collaboration is established.

Quality & Regulation Biologics

4. Scope of Site Inspection

- Personnel- Organization
- Facilities and Equipment (Warehouses, production areas, QC laboratories, utilities, animal house, etc)
- Quality systems including GMP
- Production process
- In process controls
- Quality control facilities, equipment and methods
- Stability data
- Un supply related aspects

Quality & Regulation Biologics

Preparing for the inspection

How do you think the inspection is conducted?

Quality & Regulation Biologics

Opening session

Higher management representation and HOD plus other relevant staff are present at the opening meeting

Company introduces management and senior staff

Staff makes presentations as requested on the audit agenda: usually description and plans of the site and relevant buildings, facilities lay outs, production process flow and related tests, quality system in place, etc

Presentations can be delivered by responsible staff

After the meeting, usually there will be a tour of the facilities

Quality & Regulation Biologics

The inspection: Facilities and Equipment

Aspects normally reviewed:

Quality of construction, personnel, product, materials, wastage and process flows

Utilities (HVAC, water systems, clean steam, compressed air)

Clean rooms, Classification, Pressure differentials (pressure gauges on site, alarm system)

Equipment qualification: DQ, IQ, OQ and PQ. Protocols and reports

Equipment calibration and verification. Records

Validation of computerized system. Protocols and reports

Quality & Regulation Biologics

Note: List is not comprehensive

The inspection: Organization and personnel

Aspects normally reviewed:

- Organization chart, independence of QC, QA from production Production does not direct the orchestra, rather QA does
- Roles and responsibilities of managers in major areas (production, QC, AW, maintenance, engineering, etc)
- Adequate number of personnel for each area with adequate qualifications and experience. Job descriptions, qualification records
- Health and Hygiene: regular health check ups, appropriate gowning for each task and gowning procedures, qualification of gowning procedures, safety measures, etc ….and records
- Training: Training records

Quality & Regulation Biologics

Note: List is not comprehensive

The inspection: Quality System

Aspects normally reviewed:

- Quality assurance unit, roles and responsibilities, staffing (number and qualifications)
- Documentation system, documentation and records management system
- Data Integrity assurance mechanisms
- Training program
- Vendors management
- Lot release system
- Complaints and AEFI management
- Recall, returns and destruction procedures

Quality & Regulation Biologics

The inspection: Quality System (2)

Aspects normally reviewed:

- Deviations management including investigations
- CAPA system
- Change Management
- Equipment Management including validation and maintenance programme
- External inspections management
- Data management
- Internal audits
- QRM
- APQR
- Quality Review System
- Ongoing stability programme

Quality & Regulation Biologics

The inspection: Production System

Aspects normally reviewed:

Media preparation area and process

Bulk production area and process

Storage areas

In process controls

Change over procedures

Environmental monitoring

Gowning procedures

Cleaning procedures

Formulation and filling

Quality & Regulation Biologics

The inspection: Production System (2)

Aspects normally reviewed:

Inspection of final containers
Labeling, Packaging and Shipping procedures
Change over procedures
Change Control
Handling of Deviations
Procedures, Process and systems validation
Sanitation and hygiene: Cleaning validation
Batch manufacturing records
Re-work policy

Note: List is not comprehensive

Quality & Regulation Biologics

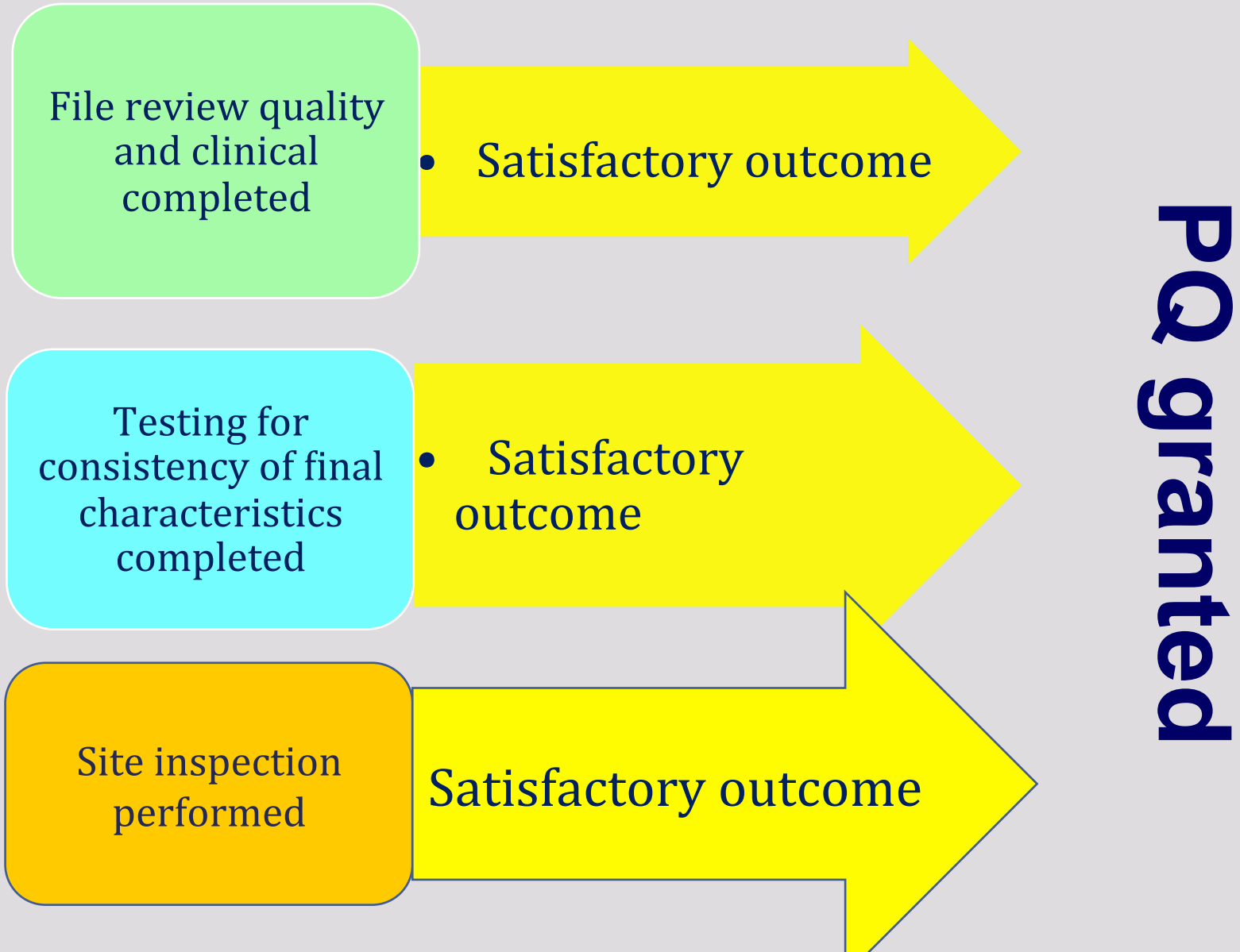
The inspection: Quality Control System

- Testing methods in place and their validation
- Tests for intermediates and final products
- SOPs, records, management of samples and data
- Data integrity assurance mechanisms
- Stability Program
- Documentation control
- Quality control facilities and equipment, including animal house
- Test results and trends- Handling of out of specifications
- Re-testing policy

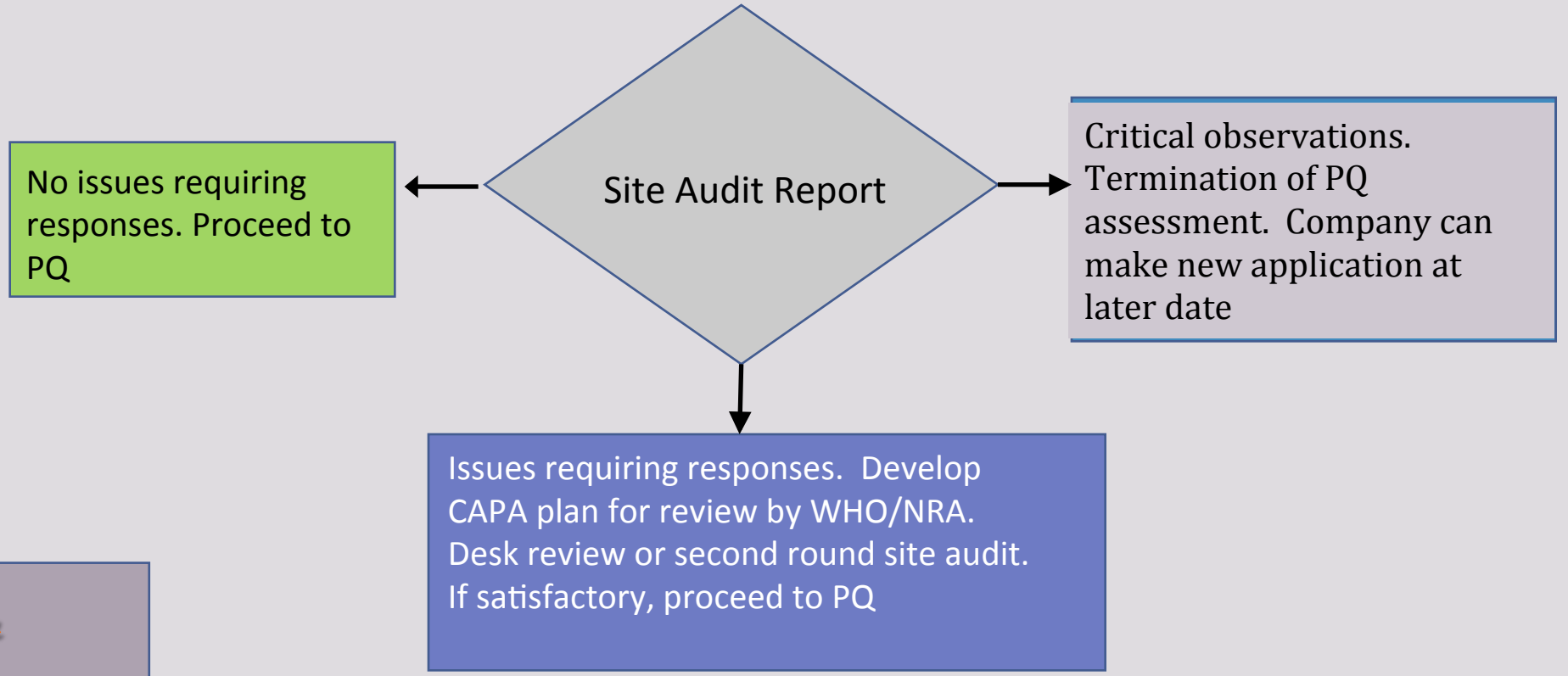
Quality & Regulation Biologics

Note: List is not comprehensive

Finalization of the process



Site Inspection Outcome



Quality & Regulation Biologics

Post-inspection phase

Addressing the observations

- Convene all relevant staff and thoroughly discuss the outcome
- Develop a serious CAPA with timelines for completion, which will include an analysis of financial implications in addition to technical feasibility
- Submit the CAPA plan within agreed timeframe
- Complete the plan according to agreed timeframe or communicate the reasons for delays if they occur

Quality & Regulation Biologics

What do you think are key elements for a successful inspection?

Quality & Regulation Biologics

Key elements for success

High commitment from management to Quality Products and to implementation of Quality Systems

Regular Quality Review Meetings, consider using quality metrics for key performance indicators

Full independence between production, Quality Control and Quality Assurance. **Quality Assurance has last word**

Transparency and honest approach to inspections

Sound and controlled documentation system, detailed procedures (SOPs), detailed records (BPR and other)

Qualified and well trained staff in all areas

Presence of QA in production, major role in review of records, investigation of deviations, internal audits and CAPA system

QC and QA dimensioned and equipped to match production capacity in volume and diversity of products

Data integrity insurance mechanisms

Quality & Regulation Biologics

What do you think are key elements for a failed inspection?

Quality & Regulation Biologics

Main reasons for failure

- Lack of commitment from management to Quality
- Roles and responsibilities at different levels not well defined
- Wish to rush products into the market without enough process robustness and experience
- Weak QA, weak quality systems in place not matching production needs
- Production head or directors' driven show
- Lack of transparency and honesty with auditors
- Lack of capacity to ensure integrity of data

Quality & Regulation Biologics

Post- PQ monitoring of compliance

- Provide PQ Vaccine Assessment Reports (PQVARs) on annual basis
  - Number (and type) of variations
  - Product safety updated reports (PSURs)
  - Lots rejected, released.
  - Testing results from ongoing stability studies
  - Complaints/AEFIs
  - Production and distribution data
  - GMP inspections related to the prequalified product
- Compliance with post-PQ commitments (i.e additional clinical data, surveillance info on safety, etc)

Quality & Regulation Biologics

Variations

Approval letter for PQ indicates need for manufacturers to inform WHO regarding variations

Three classes of variations:

- Prior Approval
- Annual Reporting
- Notifications

Guidance on variations is available at

- http://who.int/immunization_standards/vaccine_quality/variations_pq_vaccine/en/

Quality & Regulation Biologics

Risk based reassessment frequency

Uses data from PQVAR

Parameters:

- Lots rejected, released.
- Number (and type) of variations
- Interruption of production (reasons)
- Complaints/AEFIs
- WHO experience: Number of years PQed, number of PQed products, last WHO satisfactory audit, suspensions/ warning letters
- Results of lots subject to independent targeted testing programme
- Volume of supply and number of other suppliers
- NRAs: time of assessment as functional, agreements signed, responsiveness, oversight

Quality & Regulation Biologics

Targeted testing program (1)

- ✓ Independent testing of vaccine lots supplied to UN
- ✓ Testing performed by contracted laboratories performed on annual basis

  http://www.who.int/immunization_standards/vaccine_quality/contracted_labs_vaccines/en/

- ✓ Manufacturers informed in PQ approval letter of required number of samples (vaccine dependent) to be retained from each batch of vaccine supplied through UN agencies.
- ✓ Manufacturers provide list of batches supplied through UN agencies
- ✓ Three to five lots selected by WHO and samples requested from the manufacturer.

Quality & Regulation Biologics

Targeted testing program (2)

- ✓ Manufacturers to provide lot summary protocols and the NRA/NCL release certificate with each batch of vaccine submitted for testing
- ✓ In the event of out of specification results:
  - Manufacturers will be informed of test results
  - Investigation launched and applicable follow up actions, depending on result of investigation
- ✓ As required, discuss with stakeholders (UN procurement agencies, the NRA of record, manufacturer) and provide written final report of the outcome of investigation

Quality & Regulation Biologics

Responding to complaints and AEFI

As part to WHO's commitments as the advisory agency on quality, safety and efficacy of vaccines to UN agencies, the WHO/PQ team is responsible for assisting countries in the investigation of technical complaints and reports of AEFI.

- Investigation includes identification of most likely root cause
- Assisting the country/ies to investigate the case/s and to communicate with the public in case of serious AEFI
- Feeding back to purchasing agency on outcome of the investigation and recommended actions
- Information about complaints and AEFI posted on WHO website

Quality & Regulation Biologics

Thank you
谢谢
Merci
Спасибо
شكراً
Gracias
Grazie
Danke Schön
Obrigado