International Procurement and supply Schemes Part I

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

- What is it?
- Principles
- Standards- Difference with NRA
- Aspects considered
- Prequalification steps
- Contents of the dossier
- Testing of samples

Quality & Regulation Biologics

Vaccine Supply mechanisms

Domestic Production and Supply

Direct Procurement through national and/or international tendering process

UN supply (UNICEF, WHO, PAHO)

Other international procuring agencies (GAVI, MSF, Global Fund, UNHCR, UNDP, etc)

Combined mechanisms

- → domestic production + direct procurement
- → domestic production + UN agency or other International agency
- → direct procurement + UN agency or other

Quality & Regulation Biologics

What do you think are aspects to be considered in deciding the purchase of vaccines?

- Accurate demand forecast
- Accurate supply forecast by the proposer
- Affordable prices
- **Quality and safety of products (std used, source, labelling and inserts, samples)**
- **Packaging conditions (weight and volume)**
- **Lead time for supply**
- **Remaining shelf life**
- Performance of proposer (experience in supply and delivery, past performance record)
- Proposed quantity (reasonable compared to past record?)
- Warranties, intellectual property infringement, full right to sell, etc

Quality & Regulation Biologics

Ensuring quality and safety of products

- ✓ How do individual countries ensure the quality and safety of products they buy?
- ✓ How do procurement agencies ensure the quality and safety of the products they buy?

Quality & Regulation Biologics

UN Supply: Uses WHO Prequalification as the mechanism to ensure quality and safety of the products they buy

Quality &
Regulation
Biologics

What do you understand for WHO prequalification

- What is it?
- What does the term mean?
- What is it for?
- What product categories does WHO prequalify?
- Which markets does it apply to?
- Does WHO prequalify manufacturers or products?

Prequalification: The term

Scientific review

- From the wider population of a certain product category select those that meet the required standards of quality, safety and efficacy

Pre-selection: Pre-qualification

- This pre-selection of "eligible" or "acceptable" products leads to the PRE-QUALIFICATION status

Final selection= Qualification

- Procurement agencies further qualify the pre-qualified products for purchase based on additional criteria such as
- price, lead times for supply, compliance with commitments, experience with the mfg, etc

Quality & Regulation Biologics

WHO Prequalification: Its objectives

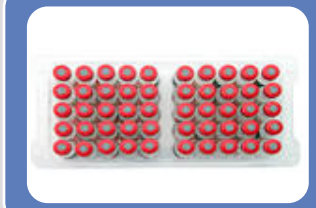
Facilitate access to adequate supply of high quality medicines to member countries

Quality & Regulation Biologics

Prequalification: Means to accomplish its objective

Provide advice to UN agencies on the quality, safety and efficacy of vaccines for purchase

By assessing the acceptability, in principle, of vaccines for purchase by Unites Nations Agencies: Vaccines Prequalification Program



By continuous monitoring of quality and compliance with the established specifications

Quality & Regulation Biologics

Prequalification: product categories assessed

Medicines: only for TB, malaria and HIV

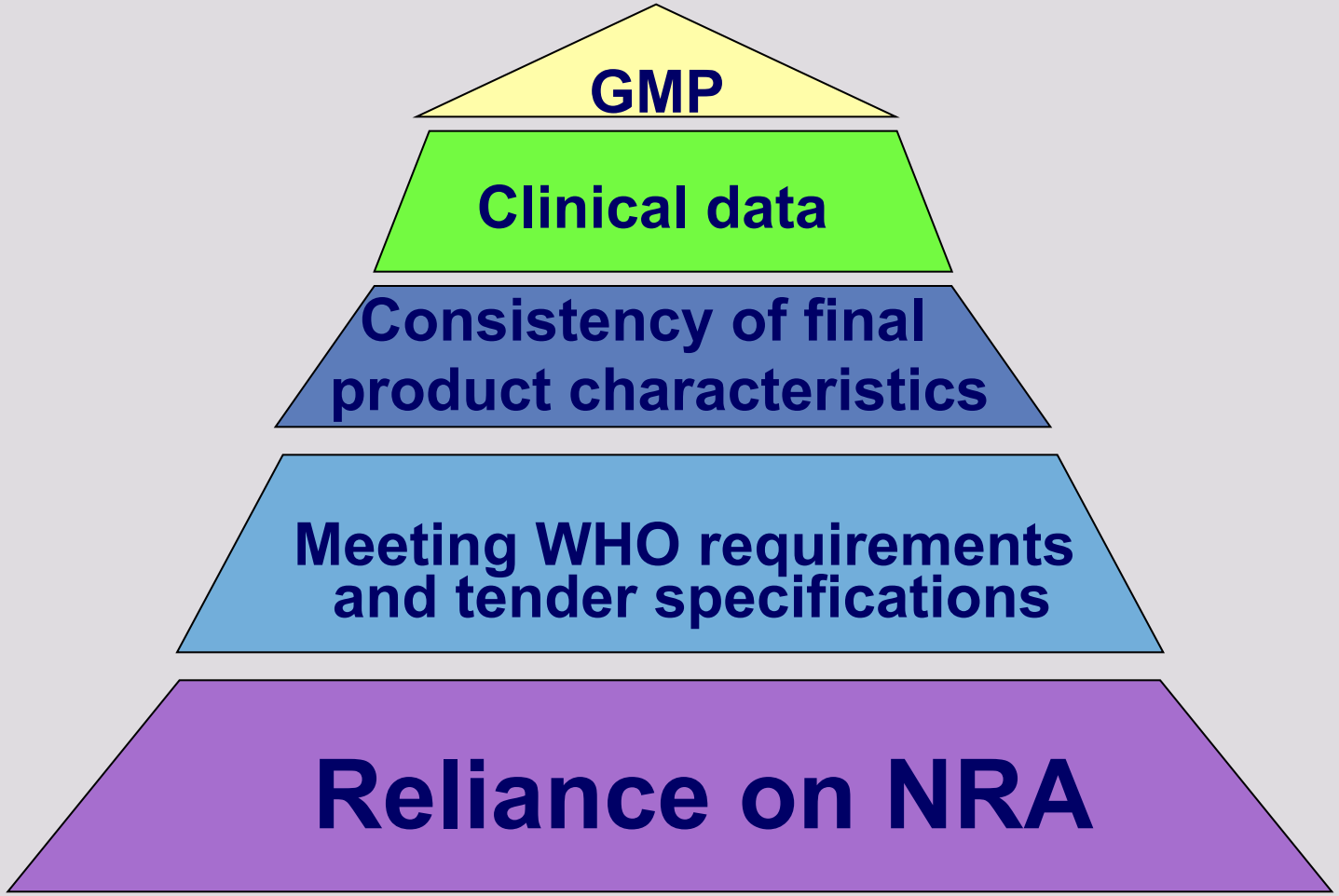
Vaccines: all those used in National Immunization Programmes for children and now expanding to other age groups

(e.g. influenza. HPV, meningococcal conjugate, malaria, etc)

Diagnostic kits

Quality & Regulation Biologics

Prequalification of vaccines: Principles



Quality & Regulation Biologics

In what ways is WHO/PQ different from a national product registration by the NRA?

Quality & Regulation Biologics

Main differences between licensure and Prequalification

Producing country NRA

- Reviews data that are relevant to their own population and conditions
- They focus on the immunization schedules relevant in their country
- Product characteristics should meet the national requirements
- Review pre-clinical and clinical data in addition to quality and safety
- Overall, they ensure that the product is safe and effective for use in the conditions of their country

WHO-PQ

- Ensures that the data provided are relevant globally
- They focus on WHO recommended schedules
- Ensures that product characteristics meet WHO recommended standard and are compatible with conditions and needs in LMICs and LICs
- Review clinical, quality and safety data and rely on NRA for review of pre-clinical data
- Overall, they ensure that the product is safe and effective for global use and that it meets the needs of NIPs in LMICs and LICs

Quality & Regulation Biologics

WHO expected standard

- **NRA in the producing country is responsible for the regulatory oversight of the product** including registration, approval of variations, GMP inspections, review and approval of non-clinical and clinical protocols and clinical data, ensuring that quality specifications are met (testing and lot release) and monitoring of post-marketing performance.
- **Reliance on NRA** of country of origin
- **NRA has to be found functional** when assessed against the WHO assessment tool by an international team of experts
- **Functionality has to be sustained over time**
- **Vaccine has to be licensed by NRA** in the producing country
- Vaccine meets WHO recommended standards of quality and safety
- **Manufacturer complies with WHO recommended GMP and Quality Systems** are adequately implemented
- **Vaccine is listed as a priority** for WHO and UN agencies

Quality & Regulation Biologics

Specific aspects considered

- General understanding of production process and quality control methods
- Production consistency at commercial scale (assessed by testing of samples of final product)
- Compliance with GMP
- Compliance with WHO recommendations and UN tender specifications including labels and inserts
- Programmatically suitable presentation
- Clinical data relevant for the target population in the recommended schedules
- Packing and transportation conditions

Quality & Regulation Biologics

Definitions

What is GMP?

What is a Quality System ?

What is Quality Assurance?

Quality &
Regulation
Biologics

Some definitions

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

Some definitions

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

Some definitions

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

What are the steps involved in prequalification of vaccines?

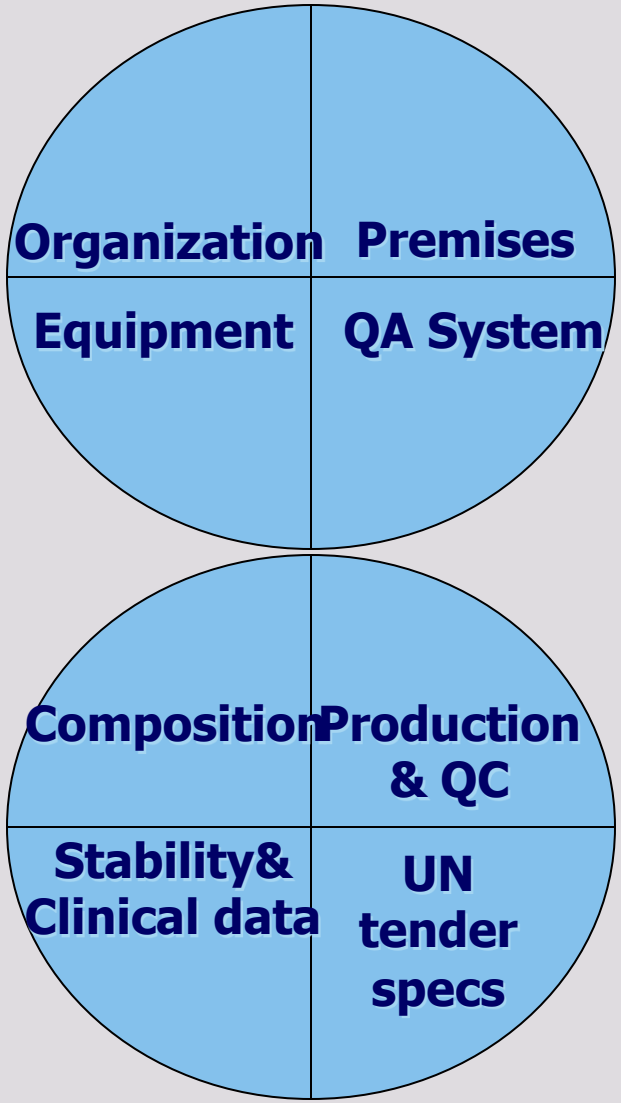
Quality & Regulation Biologics

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

1. Product Summary File



Manufacturing conditions

Product

1. Product Summary File (10 chapters)

- Chapter 1: General information
- Chapter 2: Personnel
- Chapter 3: Premises and equipment
- Chapter 4: Vaccine composition
- Chapter 5: Production process
- Chapter 6: Quality control
- Chapter 7: Stability data
- Chapter 8: Clinical experience
- Chapter 9: Production and distribution data
- Chapter 10: Regulatory actions

Quality & Regulation Biologics

Chapter 1: General information

- Information on the company
- Pharmaceutical and non Pharmaceutical activities
- Site, employees
- Outside technical assistance
- Quality Assurance system
- Quality management system
- Internal audit system

Quality & Regulation Biologics

Chapter 2: Personnel

- Organizational chart
  - Independence between Quality operations and manufacturing
- Qualifications, experience, responsibilities
- Training in GMP, SOPs, on the job training, etc
- Health requirements (Immune status, eye sight, etc

Quality & Regulation Biologics

Chapter 3: Premises and equipment

- Description of manufacturing areas
- Construction and finishes
- Flows (personnel, materials, product, waste)
- Ventilation systems
  - Classification of Clean Rooms
  - Environmental monitoring
- Water and clean steam

Quality & Regulation Biologics

Chapter 3: Premises and equipment

- Maintenance
- Description of equipment
- Procedures for change over and campaigning
- Qualification, validation and calibration
- Written specification and procedures for cleaning areas and equipment

Quality & Regulation Biologics

Chapter 4: Vaccine composition

- Composition (vaccine and diluent)
- Presentations
- Recommended schedule
- Labels, boxes, inserts — WHO recommendations
- Summary protocols — WHO format

Quality & Regulation Biologics

Chapter 5: Production

- 5.1 Manufacturing formula
- 5.2 Description and flow chart of Manufacturing & testing
- 5.3 General policy for process validation
- 5.4 Handling of starting materials, packaging materials, bulk and finished products (Sampling, quarantine, release and storage).
- 5.5 Handling and procedures for destruction of rejected materials and products.

Quality & Regulation Biologics

Chapter 6: Quality Control (1)

- 6.1 Starting material
  - 6.1.1 Raw material
  - 6.1.2 Labelling and packaging
  - 6.1.3 Qualification of suppliers
- 6.2 Intermediate products
  - ✓ 6.2.1 Specifications and routine tests
  - ✓ 6.2.2 Methods Validation

Quality & Regulation Biologics

Chapter 6: Quality Control (2)

- 6.3 Finished product
  - 6.3.1 Specifications and routine tests
  - 6.3.2 Validations
  - 6.3.3 List of Rejected Lots

Quality & Regulation Biologics

Chapter 7: Stability data

- ✓7.1 Intermediate products
- ✓7.2 Finished product : vaccine
- ✓7.3 Finished product : diluent & reconstituted product
- ✓7.4 Policy for assigning the date of manufacture of each component, final product and diluent

Quality & Regulation Biologics

Chapter 8: Clinical experience

Note 1 : Reference documents

- TRS 978, Annex 6 (2012, PQ procedure) http://www.who.int/entity/immunization_standards/vaccine_quality/TRS_978_61st_report_Annex_6_PQ_vaccine_procedure.pdf
- TRS 850 (1995, GCP); http://apps.who.int/prequal/info_general/documents/TRS850/WHO_TRS_850-Annex3.pdf
- TRS 924 (2004; clinical evaluation of vaccines); http://who.int/entity/biologicals/vaccines/clinical_evaluation/en/index.htm
- TRS 927 (2005; non-clinical evaluation of vaccines) http://who.int/biologicals/vaccines/nonclinial_evaluation_of_vaccines/en/
- Points to consider for manufacturers of human vaccines: clinical considerations for evaluation of vaccines for prequalification http://www.who.int/immunization_standards/vaccine_quality/pq_vaccine_evaluation/en/
- Vaccine specific TRS as applicable

Quality & Regulation Biologics

Chapter 8: Clinical experience

Note 2

For vaccines originally licensed many years before application for prequalification, emphasis should be given to document history of safe and effective use.

Note 3

Provision for request of raw data

Quality & Regulation Biologics

8.2 Clinical trial information (1)

- √ 8.2.1 Applicant's sponsored clinical trial overview
  - List of all clinical trials conducted (in all countries relevant to the application for WHO PQ)
    - For each study sponsored by the applicant (before and after initial licensure)
      - Approved protocol (by NRA and Ethics Committee)
      - Evidence of registration in a CT registry (WHO ICTRP)
      - Compliance with GCP

Quality & Regulation Biologics

8.2 Clinical trial information (2)

- √ 8.2.1 Applicant's sponsored clinical trial overview (cont'd)
  - For each study, to be provided (in a table or brief summary)
    - Type of study
    - Rationale
    - Study sites
    - Dates
    - Statement of final conclusions
    - Copies of publications and abstracts to be provided
  - List of ongoing trials
    - Details of the study plan
    - Expected date of results

Quality & Regulation Biologics

8.2 Clinical trial information (3)

- ✓ 8.2.2 Other studies with the applicant's product
  - ✓ Not sponsored by the applicant
  - ✓ Vaccine as intervention of main interest or used as comparator
  - ✓ Also observational studies (e.g. case-control studies)
  - ✓ Identified by literature search

- ✓ 8.2.3 Clinical summary – (similar to CTD 2.5)
  - ✓ Detailed summary and interpretation of the safety and efficacy data of all studies (pre- and post-licensure)
  - ✓ Relevance to support worldwide use
    - ✓ WHO recommended schedules
    - ✓ Co-administration with other vaccines
  - ✓ Expected to complement (not replace) the summary written by an independent clinical expert (8.2.5)

Quality & Regulation Biologics

8.2 Clinical trial information (4)

√ 8.2.4 Assessment reports

– Whenever possible

- Clinical section of the national regulatory authority (NRA) assessment report from the country of origin and/or country where initially licensed
- Assessment reports for any subsequent variations to the license for changes relevant to clinical data
- Assessment reports from other NRAs

Quality & Regulation Biologics

8.2 Clinical trial information (5)

- ✓ 8.2.5 Clinical expert report
  - Independent clinical expert report
    - Evidence of expertise and independence to be provided
  - Particularly useful for products licensed long time before
    - Limitations put in the context of the requirements at the time of licensure
      - Ethical approval / GCP
      - Study design / sample size
    - Impact on disease control after introduction in vaccine programme
    - Post-marketing safety data

Quality & Regulation Biologics

8.2 Clinical trial information (6)

- √ 8.2.6 Preclinical studies sponsored by the applicant
  - List of all preclinical studies sponsored by the applicant (TABULATED FORMAT)
  - For preclinical studies performed after initial licensure, indicate the reasons for these studies

Quality & Regulation Biologics

8.3 Documentation on safety (1)

- √ 8.3.1 Pharmacovigilance plan
  - Introduced in the current PQ procedure (from 2012)
  - Important to determine whether it is planned to generate evidence to support the use of the product in different populations (geographical areas, age groups, etc…) Some evidence will be expected as a post-prequalification commitment

Quality & Regulation Biologics

8.3 Documentation on safety (2)

- √ 8.3.2 Initial evaluation of vaccines that have been in the market for a long time (or reassessment of already prequalified vaccines)
  - Outline of the applicant's procedures for the collection, onward notification and assessment of adverse events
  - Listing of all reported AEFIs
  - Periodic Safety Update Reports (PSURs) may provide all the information needed
    - ICH format preferable

Quality & Regulation Biologics

8.3 Documentation on safety (3)

- √ 8.3.3 Recently licensed vaccines
  - – Ongoing phase IV studies
  - – Ongoing active monitoring of the safety profile
- √ 8.3.4 Documentation of serious advent events
  - – Fullest possible description of each case, including any information there may be on investigations, actions, patient treatment and outcome
  - – Periodic Safety Update Reports (PSURs) may provide all the information needed

Quality & Regulation Biologics

Outcome of the review of PSF

Scenario 1: PSF review does not raise any outstanding issues	Consistency testing is scheduled
Scenario 2: PSF review raises outstanding issues for clarification/additional information (not major)	Outstanding issues may be followed up at site audit &/or request for additional information Consistency testing is scheduled
Scenario 3: PSF review raises major technical and programmatic issues	Ad Hoc committee is convened Request for additional information to give final recommendation or stopping the PQ

Quality & Regulation Biologics

2. Testing

- When the review of the file is complete, samples are sent for testing
- Samples from 3 consecutive lots of the vaccine provided to WHO
- WHO sends the samples to usually two collaborating laboratories for testing of final product characteristics
- Usually, only the most relevant tests are performed on final product. E.g. potency testing.

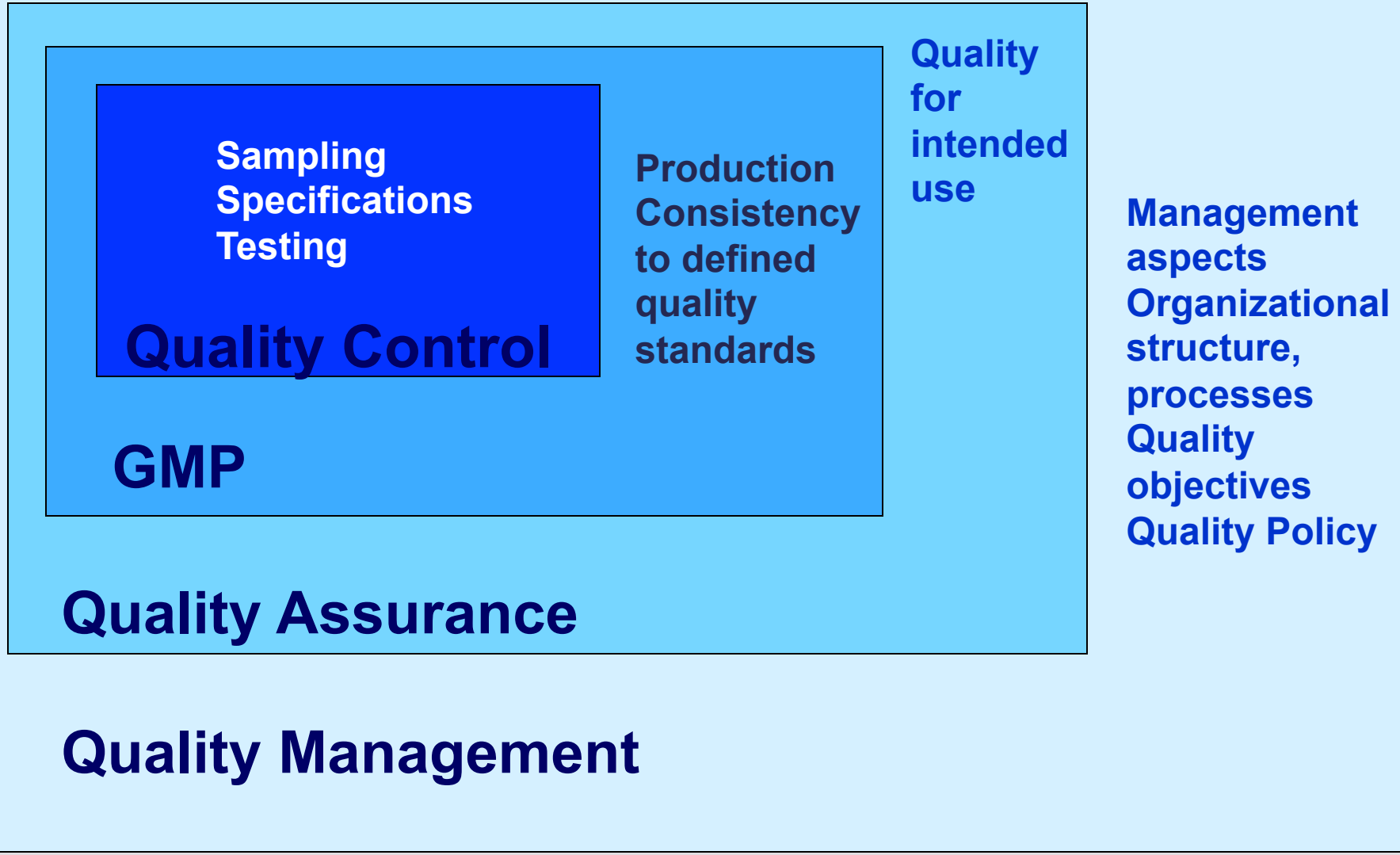
Quality & Regulation Biologics


THANK YOU

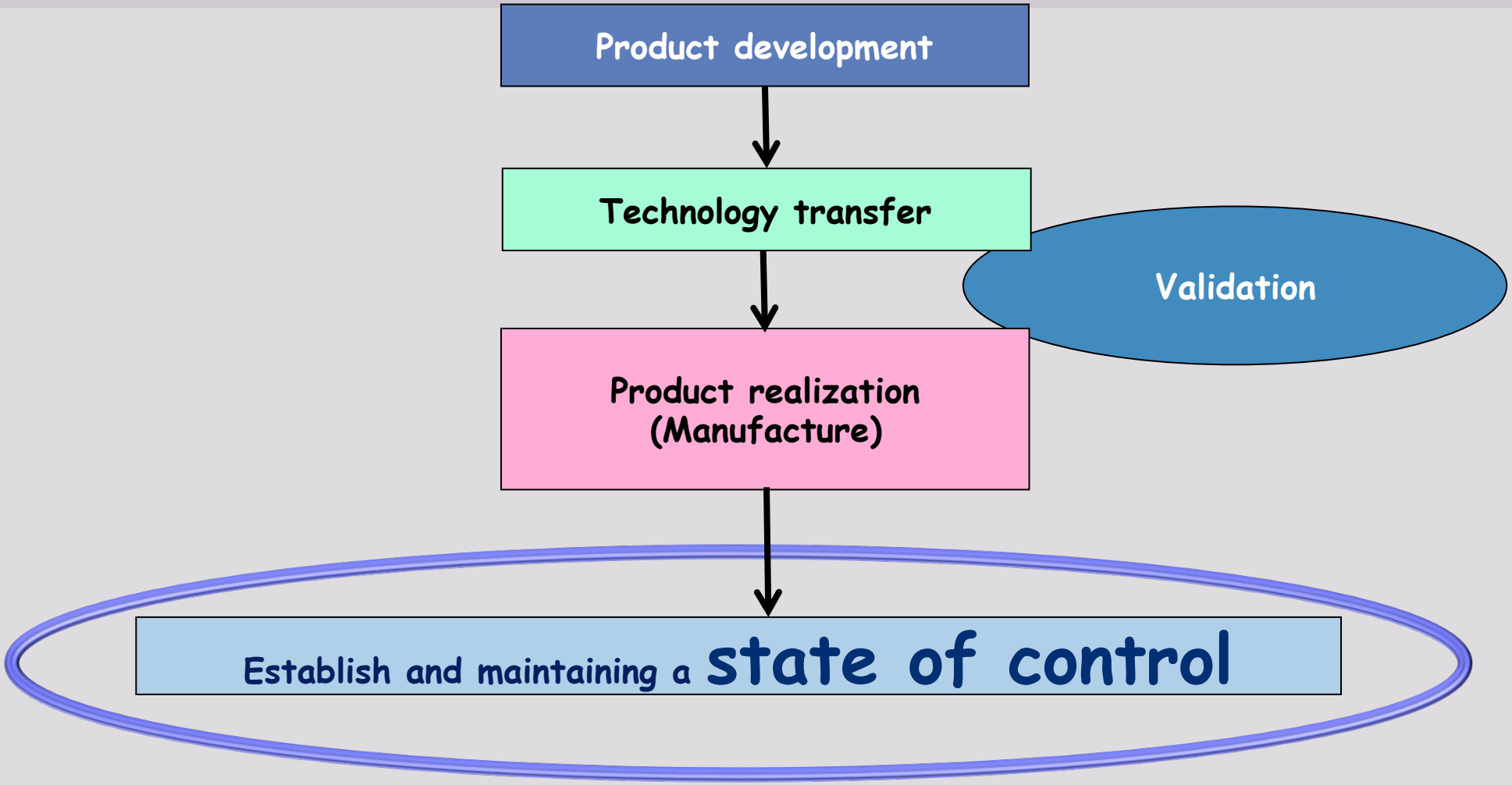
Back up slides

Quality &
Regulation
Biologics

Quality Relationships



What's the company's aim?



How to keep it?

State of control
=
CONSISTENCY

Monitoring process performance
(quality management indicators & trend analysis)

Monitoring product quality
(product quality review or PQR)

Change management system

Corrective action and preventive action (CAPA) system