Polpharma

Regulatory, Manufacturing and Supply Chain Aspects

Session 5: Supply Chain Management and Surveillance

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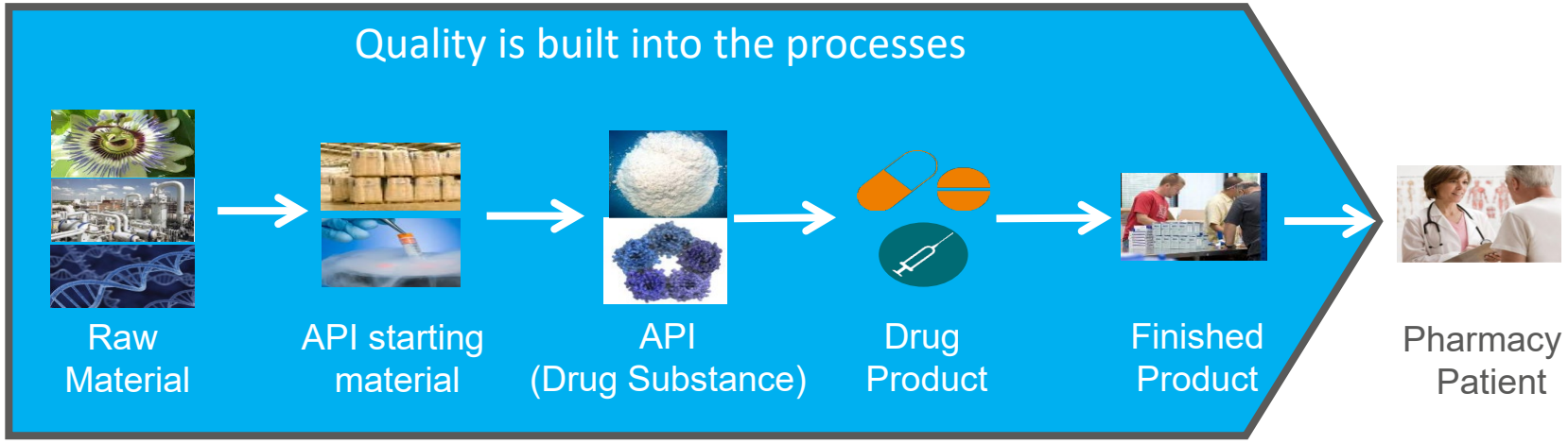
EMA Sartans with N-nitrosamine impurities
Lessons Learnt Exercise - Interested Parties Meeting
Amsterdam, 04. November 2019

Medicines are well Developed, Manufactured and Available for Supply



Quality Agreements between actors in the supply chain

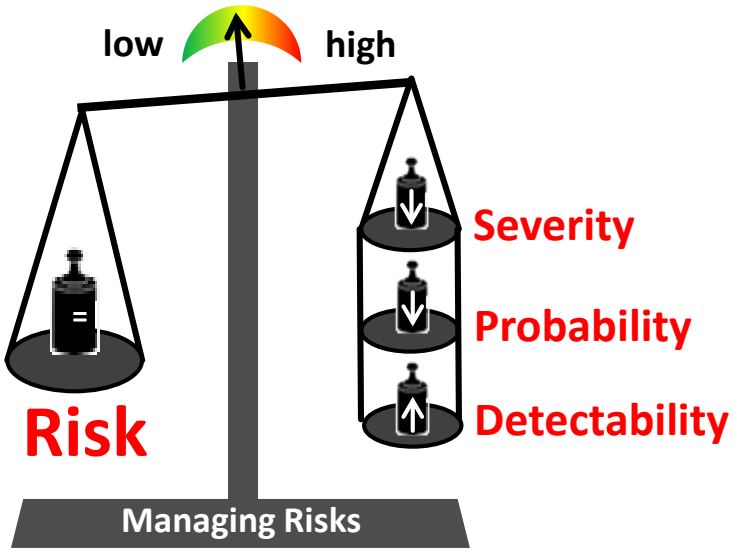
=> GMP responsibilities

=> Quality measures of each party

Fundamental Strategies in Operations:
Recognise Risks are Managed at a Desired Level

- **Achieving anticipated quality**
  - Using good science
  - Realising solid risk assessment
  - Implementing Good Manufacturing Practices

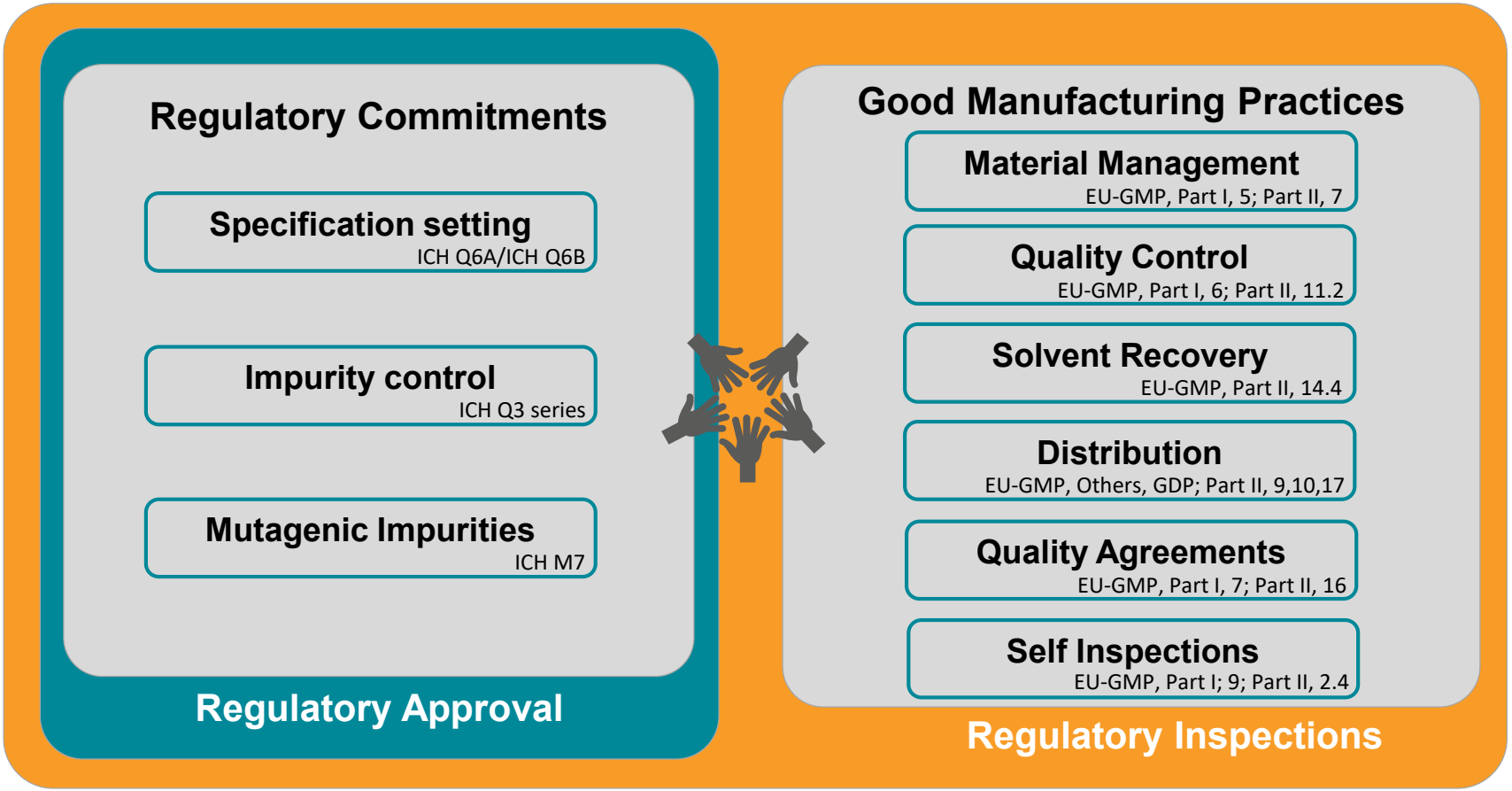
- **Ensuring quality targets are achieved**
  - Applying defined controls as necessary
  - Improving with preventive actions
  - Analysing on a solid understanding of root causes if something happens



Quality Risk Management: ICH Q9 briefing pack https://ich.org/page/briefing-pack

The Regulatory Framework has Established Controls:

All European Pharmaceutical companies are bound to fulfill, otherwise they can not operate



ICH: International Council for Harmonisation: implemented into the EU regulatory framework
EU-GMP Part I for medicinal products; EU-GMP Part II for Active Ingredients

The Regulatory Framework and Established Controls already exists: Is there a need for updated guidance?

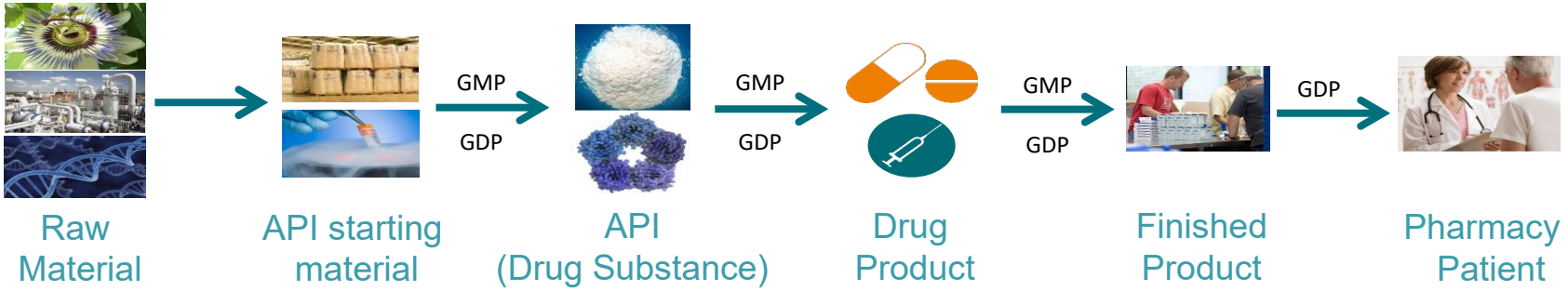
Quality Systems and Control Process	Supplier Management Process	Supply Chain Management Processes (examples)
• Impurities are controlled at the validated level • Cleaning validation in shared factifies	1. Selection 2. Qualification & Development 3. Monitoring & Managing	• Quality Monitoring • Change Management • Awareness of hazards, assessment and control of risks

- **Quality Risk Management (QRM) is established**

  ⇒ Companies use QRM to identify hazards and mitigate the risks

  ⇒ Subjected to regulatory oversight

Applied Quality Risk Management in Operations:
Risks Can be Controlled - Residual Risk Remains



- **Analytical techniques and specifications are appropriate**

  => New knowledge, experience and expectations will be taken into account

- **Processes are controlled and monitored**

  => Procedures assure the recovered materials meet suitable specification

- **Recognise risks at a desired level**

  => Adoption of the risk control is possible - A zero risk scenario is not possible

- **Quality Agreements** between actors in the supply chain define the **GMP responsibilities** of each party
- **Analytical** techniques and specifications are **appropriate**
- **Processes** are **controlled** and **monitored**
- Recognise risks at a desired level: **zero risk scenario is not possible**
- **Inspections** & **guidelines** ensure the **regulatory oversight** in the supply chain

EU API MANUFACTURERS APPROACH

- **API manufacturers are systematically performing genotoxic assessments that includes nitrosamines (as structural alerts) in the scope of evaluation, according to ICH M7**
- **Adoption of EMA request for risk evaluation of the presence of nitrosamine impurities: API manufacturers have adopted the guide for RA evaluation based on**
  - Production process evaluation
  - Starting materials sourcing
  - Solvents and reagents

AESGP APIC 25 years of promoting patient safety active pharmaceutical ingredients committee efpia European Federation of Pharmaceutical Industries and Associations EUCOPE European Confederation of Pharmaceutical Entrepreneurs AISBL medicines for europe better access. better health.

API production process

- Understanding of formation and purge of impurities
- Cross contamination (equipment); cleaning validation/ dedicated equipment

Starting materials

- Process knowledge
- Supplier commitment for changes communication
- Supplier evaluation and risk assessment
- On site audits

Raw Material

(Solvents/Reag Catalysts)

- Supplier evaluation
- In house recovery
- External recovery; supplier information and on site audits

RISK ASSESSMENT

RISK ASSESSMENT OUTPUT

NO RISK/ ACCEPTABLE LEVEL OF RISK	CONFIRMATORY TESTING	RISK REDUCTION
• No action required	• Need to test before final evaluation • Method development and validation	• Routine test implementation • Process change • Variation

Key point is prioritization based on real risk, focusing on high risk API:

- Sartans
- Other APIs with tetrazole ring
- Amines and nitrites concomitantly used in the synthesis
- Other APIs