GMP considerations when designing an API plant

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Regulatory Knowledge, Practically Applied.

Introduction

API manufacturing is too broad a topic to cover all scenarios so I will draw from recent projects I have been involved in.

Common drivers:

- Scale up from pilot plant to commercial production
- GMP compliance
- Biological starting material
- Renovation of existing facility

Active Pharmaceutical Ingredient

WHO definition of Active Pharmaceutical Ingredient:

"**A** substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological function to human beings"

Relevant GMP's

ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (November 2001) (under revision)

ICH driver:

- "wide implications of this topic"
- "formalise GMP requirements for components of pharmaceutical products – both **active** and inactive"

Based on PIC/S draft

Adopted or referenced by:

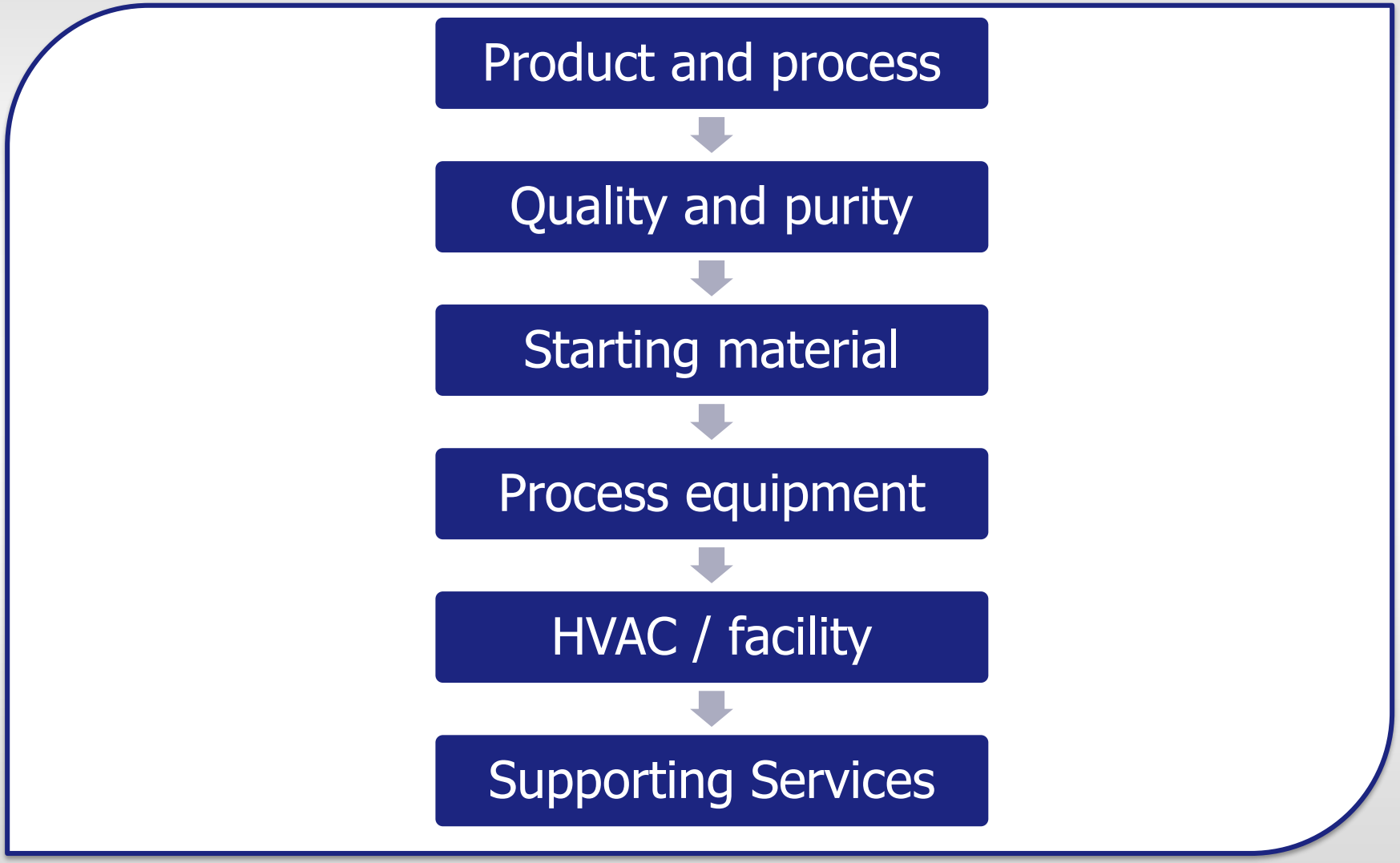
- PIC/S in 2007 - Guide to GMP PE009-11 Part II
- FDA Notice in 2001 - Vol. 66 No. 186 p. 49028-9

Relevant GMP's

More recent developments:

- ICH Question & Answer – June 2015 clarification
- ICH Q11: Development and Manufacturing of Drug Substances (Chemical Entities and Biotechnology / Biological Entities) – May 2012
- ISPE Baseline Guide Volume 1 Active Pharmaceutical Ingredients

Overall Design for GMP



Nature of Product and Process

Generally APIs are:

- High value
- Low volume
- Limited sources of API starting material

Therefore consider:

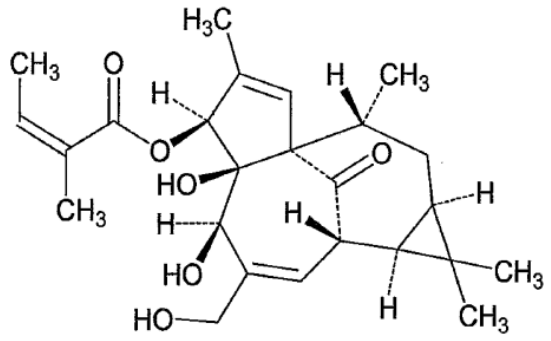
- Maximise yield
- Security measures to protect product, people and assets
- Consistent product quality
- Synthetic versus natural sources

Nature of Product and Process

Active Pharmaceutical Ingredients by their nature are active and at concentration and volume may be:

- Toxic (steroids, cytotoxic)
- Highly pharmacological activity
- Highly sensitising agent or present other hazards.

The nature of the product and process will determine the design of the process and supporting facility.



Product Quality and Purity

Finished Pharmaceutical Product may be:

- Human or veterinary
- Parenteral / sterile – need to comply with PIC/S Annex 1
- Oral solid dose
- Dermatological
- Other

ICH Q7:

- Intended specification for quality and purity
- Quality Risk Management required

API Starting Material

ICH Q7:

- GMP "boundary" starts with "introduction of API starting material into process"
- Defined in regulatory filing by the applicant and approved by the regulatory review process.
- An appropriate level of controls suitable for the production of the API starting materials should be applied

Process Equipment

Document the design process to demonstrate:

- Adequate size
- Suitably located
- Reproducible and effective cleaning (e.g. automated CIP)

Product contact equipment design considerations:

- Chemical compatibility of metallic and elastomer components
- Hygienic design appropriate for process

Avoid use of global company design standards if they are not relevant for API manufacture

Process Equipment

Closed on containment systems will:

- Reduce exposure of product to contamination
- Reduce exposure of personnel to product
- Impact facility and HVAC design

Mobile Milling Isolator

HVAC and Containment

Containment will determine appropriate controls to:

- Minimise risk of contamination and cross contamination
- Air pressure, micro-organisms, dust, humidity, temperature
- Where APIs are exposed to the environment - weighing

Facility Design

Appropriate for product and process:

- Dedicated facility for highly sensitising materials
- Equipment can be located outdoor (ICH Q7 4.12)
- Risk-based approach – activity of toxicity – exposure limits
- Facilitate cleaning, maintenance and operations
- Prevent mix-ups and contamination

Critical systems should be qualified, monitored and have drawings available

Water quality specification

ICH Q7:

- "Suitable for intended use"
- Minimum quality: drinking water

EMEA "Note for Guidance on Quality of Water for Pharmaceutical Use" Table 3 specifically for API's

In practice:

- Careful in scaling up e.g. avoid ASTM Type I
- Select the appropriate grade for the application

Conclusion

Each API manufacturing facility is unique

Facility Design depends on:

- Nature of product and process
- Selection of process equipment
- Suitable background environment

Achieving Intended specification for quality and purity

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Thank you.
Any Questions?

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