APIMAA

Active Pharmaceutical Ingredient
Manufacturers' Association of Australia

# Manufacture and Quality Requirements of NMEs / APIs for Clinical Trials

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# Points to consider for NME's moving from R&D into Clinical Trials

**TARGET**: Develop registerable commercial product

- QUALITY / SAFETY / EFFICACY requirements

**KEY RISKS**:

- Limited safety information in humans
- NME (API) production process is lab scale
- Limited characterization of NME (eg impurities, structure)
- Patents / IP protection

# RISK REDUCTION: REPRODUCIBILITY

- Comprehensively document "manufacturing" process (synthesis / purification, etc) at R&D stage:
  - Processing conditions
  - Materials
  - Equipment
  - Analytical methods & equipment
  - NME characterization (structure, activity, purity, impurities)
  - Define what is deemed to be a 'batch'

# RISK REDUCTION: R&D Process for NME

- Can R&D process be scaled up to commercial?
- Process safety concerns / OHS hazards?
- Process materials suitable for pharmaceutical use?
- Materials safety issues: unacceptable solvents, BSE/TSE, pesticides, mycotoxins, viruses, herbicides, elemental impurities? (ICH guidelines)
- Commercial scale availability of process materials?

- Avoid major manufacturing process changes at GMP stage: potential safety & efficacy impact, rejection of IND

# RISK REDUCTION: DOCUMENTATION

- Good documentation:
  - allows thorough investigation of any failures
  - facilitates process improvements & tech transfer
  - documents that you have taken 'due care'
  - Legal Liability: "If it is not documented it was not done"

# RISK REDUCTION: SAFETY

Key risk for NME in first in human (phase 0/1) studies:

no previous human safety knowledge

- Australian legislation exempts 'initial experimental studies in human volunteers' from GMP compliance

BUT

- Is ignoring GMP principles worth the risk?

- Liability: "If it is documented you can prove it was done"

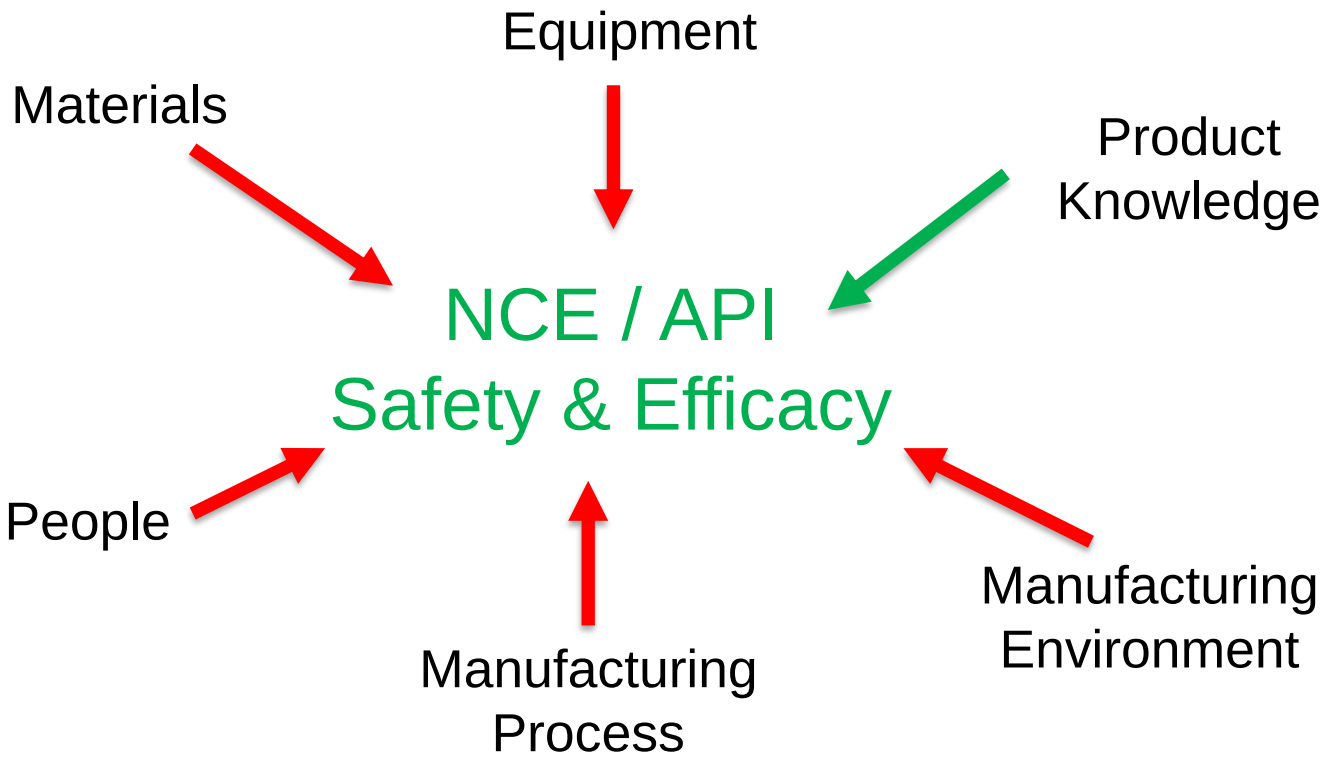
# Good Manufacturing Practice

- GMP ….. "generates more paper" (unfortunately yes)

BUT:

- Principles of GMP provide guidance for managing the highlighted risks
- Provide a structured (good science) approach for introducing and managing changes
- Key objective: ensure product quality, safety and efficacy

# KEY PARAMETERS ENSURING PRODUCT SAFETY & EFFICACY




**CHANGES MAY IMPACT ON PRODUCT SAFETY & EFFICACY**

(eg elevated or new impurities)

# GMP - Points to Consider

- Key risks to be managed: process & specification changes
- All quality activities defined and documented
- Knowledge gained in development phase documented
- Products meet pre-defined requirements for quality, purity and safety at each trial phase: SPECIFICATIONS
- Level of GMP control increases from phase 1 to phase 3
- Rationale for controls (implemented or not) documented and justified
- Deviations / OOS are expected in development phase. Investigate and gain process / product knowledge

- GMP starts with introduction of 'starting material' (FDA: propinquity rule)

# API Manufacture for Phase 0/1 Studies

**FACILITY**

- Adequate space, clean
- Contamination & cross-contamination control

**PROCESS**

- Documented 'manufacturing' process
- Adequately controlled equipment (contamination risk)
- Materials documented, draft specifications, suitable for intended use, CoA
- 'Consistency batches' R&D scale

# API Manufacture for Phase 0/1 Studies

**ANALYTICS**

- Extensive analytical testing to gain product knowledge starts in R&D
- Documented analytical methods: scientifically sound & reproducible (specific, sensitive, accurate)
- Methods developed in parallel to process development
- Qualified & calibrated analytical equipment

# API Manufacture for Phase 0/1 Studies

## PRODUCT

- Ensure purity / impurity profile is equal to or better than R&D batches used in toxicology studies
- Draft specifications (use limited set of high confidence & reliable analytical methods)
- Preliminary stability studies: cover clinical trial use period
- Sterile products: GMP requirements for sterility (process & testing)
- 'Batch' of product: defined, traceable
- 'Batch records': accurately recorded data from production & testing
- Retention samples kept for each batch
- Product Specification file initiated

# Additional Activities for Phase 2 Studies

Manufacture under GMP in licenced facility

**FACILITY**

- IQ/OQ
- Calibration & Maintenance program
- Cleaning validation (facility & process)

**PROCESS**

- Improve purity / impurity profile
- Scale up of process & increased number of batches
- Less changes, in process controls identified

# Additional Activities for Phase 2 Studies

Manufacture under GMP in licenced facility

**ANALYTICS**

- Reference Standard identified / working standard established
- Review suitability of analytical methods
- Stability indicating methods developed
- Product characterization well advanced (structure, purity, impurities)
- Commence analytical method validation

# Additional Activities for Phase 2 Studies

Manufacture under GMP in licenced facility

**PRODUCT**

- Ongoing stability trials (accelerated and real time) for materials from scaled up process
- Review available stability data: define preliminary retest date or stability period
- Container Closure System identified
- Conduct stress studies, determine degradation pathways
- Review product specifications

# Additional Activities for Phase 3 Studies

Manufacture under GMP in licenced facility

## PROCESS

- Process finalized (synthesis route / purification), defined in MBR
- In process controls defined, acceptance criteria set
- Expected process yields defined
- Scale up of process towards commercial
- Process validation planned / commenced

## ANALYTICS

- Method validation completed, acceptance criteria established, product characterisation completed

# Additional Activities for Phase 3 Studies

Manufacture under GMP in licenced facility

**PRODUCT**

- Stability trials for materials from finalized process
  - accelerated and real time, forced degradation studies, Photostability, Temperature cycling
  - Material compatibility (process & primary packaging materials)
- Review available stability data: define retest date or stability period
- Container Closure System defined and simulated in stability studies
- Impurities identified and qualified
- Review and finalise product specifications

# SPECIFICATIONS

- Must be 'fit for intended use' and justified
- Acceptance criteria
- In Process / Release / Stability
- 'Product characterization' specifications & pharmacopoeia requirements
- Product specification requirements vary depending on the intended route of administration:
  - Oral / topical / inhaled / injectable
  - Sterile vs non-sterile

# SPECIFICATIONS

- Description (solid / liquid / colour / etc)
- Identification (test must be specific for API)
- Assay / Quantity (specific for API and stability indicating)
- Impurities
  - Organic / inorganic / microbial
  - Process related (material inputs, processing aids, etc)
  - Product related (degradation products)
- Physicochemical properties
- Chemicals: particle size, polymorphics, chirality
- Biologicals: biological activity / potency, heterogeneity pattern

# FINAL CONSIDERATIONS

- Product Safety & Efficacy data generated in the clinical trials are only valid for the API manufactured and analysed by the documented and validated manufacturing process

- Changes to the manufacturing process must be demonstrated to not have any adverse impact on the safety and efficacy profile of the API