Group A

SMALL SCALE COMPOUNDING FOR INDIVIDUAL PATIENTS

Captopril Oral Liquid 1mg/ml (50ml)

HOSPITAL A

- General hospital (adults & paediatrics) with 500 beds
- Compounding areas in Pharmacy Department
- Sterile Preparation
  - Total parenteral nutrition, other aseptic preparations
- Non-sterile preparation
  - Topical preparations, oral liquids, oral dosage forms, suppositories

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INDIVIDUAL PATIENT REQUEST

- 6 month old child with heart failure
- Requires titrating dose of ACEi
- Captopril is the ACEi of choice
  - Short half life
  - Clinical experience
  - Pharmacokinetic experts
- Doctor requests advice from pharmacist

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TECHNICAL INFORMATION

- Captopril $C_9H_{15}NO_3S$
- Molecular weight 217 (BP, 2007)
- Solubility 160mg/ml at 25°C (BP, 2007)
- pKa 3.7 (carboxyl group); 9.8 (sulfhydryl group) [Kadin, 1982]
- Optimum pH stability <3.5 (Kadin, 1982)

OPTIONS

- Ward-based manipulation
  - Dissolve a tablet and take an aliquot
- Compound in pharmacy
  - Capsules
  - Liquid
  - Powders and papers
- Import from Australia (adult strength)

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WHAT SHOULD WE DECIDE TO DO?

	Advantages	Disadvantages
Ward-based manipulation	Quick	Inaccurate doses & safety, nursing time
Prepare capsules	Stability, generally accurate doses	Not easy to adjust doses, exposure to powder
Prepare liquid	Titration of doses, easy to swallow	Stability concerns
Prepare powder/paper	Quick	Exposure to powder, inaccurate, unstable
Import from Australia	Assurance of quality	Adult strength, excipients, cost, indication

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PRODUCT DESIGN

- API – Captopril powder
- Concentration 1mg in 1ml
- 1:1 Ora-Sweet:Ora-Plus
- (Or Unpreserved Syrup in newborn child)
- 50ml volume
- Amber glass bottle (Type III) with clear label
- Label –strength per ml
- Child-resistant closure (polyethylene)
- Oral syringe

- Shelf-life 7 days

  (Literature: 7-28 days)
- Life-cycle: In use but under development – possible addition of ascorbic acid to improve stability (antioxidant)
- Release criteria:
  - Visual inspection & organoleptic control
  - Label
  - Volume

SITE MASTER FILE

- Mission & Strategy
- Personnel
- Training & Competency
- Premises
- Equipment
- Quality Assurance & Quality Management System

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MISSION & STRATEGY

- “Right medicine, right patient, right time”
- We aim to provide medicines not available from industrial companies
- Provision of information for patients and healthcare professionals
- Continuing professional education of all members of staff with regard to compounding service

PERSONNEL

Production Unit

- 1 Senior Pharmacist
- 4 Pharmacists
- 5 Technicians
- 3 Operational Assistants
- 2 Student Pharmacists

Non-Sterile

- 1 Pharmacist – Head of Non-Sterile Production
- 1 Pharmacist – Quality Assurance
- 2 Technicians
- 1 Operational Assistant
- 1 Student Pharmacist
- Support from quality control department

TRAINING & COMPETENCY

- Pharmacists
  - Compounding legislation
  - Good Preparation Practice
  - Continuous professional education
  - Health & safety
  - Formulation & stability
  - Risk management
  - Product development
  - Quality management systems e.g. Standard Operating Procedures (SOP)
- Technicians & Assistants
  - Health & safety
  - Good Preparation Practice
  - Calculations
  - Continuous professional education

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PREMISES

- Compliance with national guidelines for room specifications
- Dedicated room for small scale preparation
- Uni-directional workflow
- Separate weighing area with minimum draughts and vibration
- Easy to clean
- Monitoring of temp, humidity and lighting – comfortable and limit degradation (less than 25 degrees)
- Compounding Unit:
  - Storage Room (row material and packaging materials)
  - Preparation Room
  - Administrative Room
  - Washing Room

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EQUIPMENT

- Calibrated balances & measuring cylinders
- Glassware inspected regularly and free from cracks and chips
- Separate glassware for internal and external products
- Fridges with controlled temperature monitoring
- Dedicated garments, gloves, mask and hair covers during preparation
- Anti-vibration table
- Secure storage with ventilation

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QUALITY MANAGEMENT SYSTEM

- Standard Operating Procedures - SOP
  - Weighing and measuring
  - Labelling
  - Producing worksheets
- Change control
  - E.g. change of starting materials
- Worksheets & records
- Non-conformity Policy
- Complaints & Errors Policy
- Validation & calibration of critical processes & equipment
- Computerised systems for labelling

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QUALITY CONTROL OF PROCESS

- No testing of captopril or packaging (purchase from certified supplier – Certifcates of Analysis/Conformity)
- No chemical analysis – but visual inspection
- Verification of balances
- Completed worksheet check (date, batch numbers, signatures for key steps)
- Release check

BUSINESS PLAN – ORAL LIQUIDS

- Market – stroke patients, elderly, children, patients with swallowing problems and/or feeding tubes
- Competitors – imports, ward-based manipulations, batch manufacture
- Trends – increasing demand, shortages of licensed medicines
- Consequences of not delivering – treatment failure, morbidity, cost (to buy)
- Other options – buy from another source e.g. other hospital or pharmacy, specialist supplier

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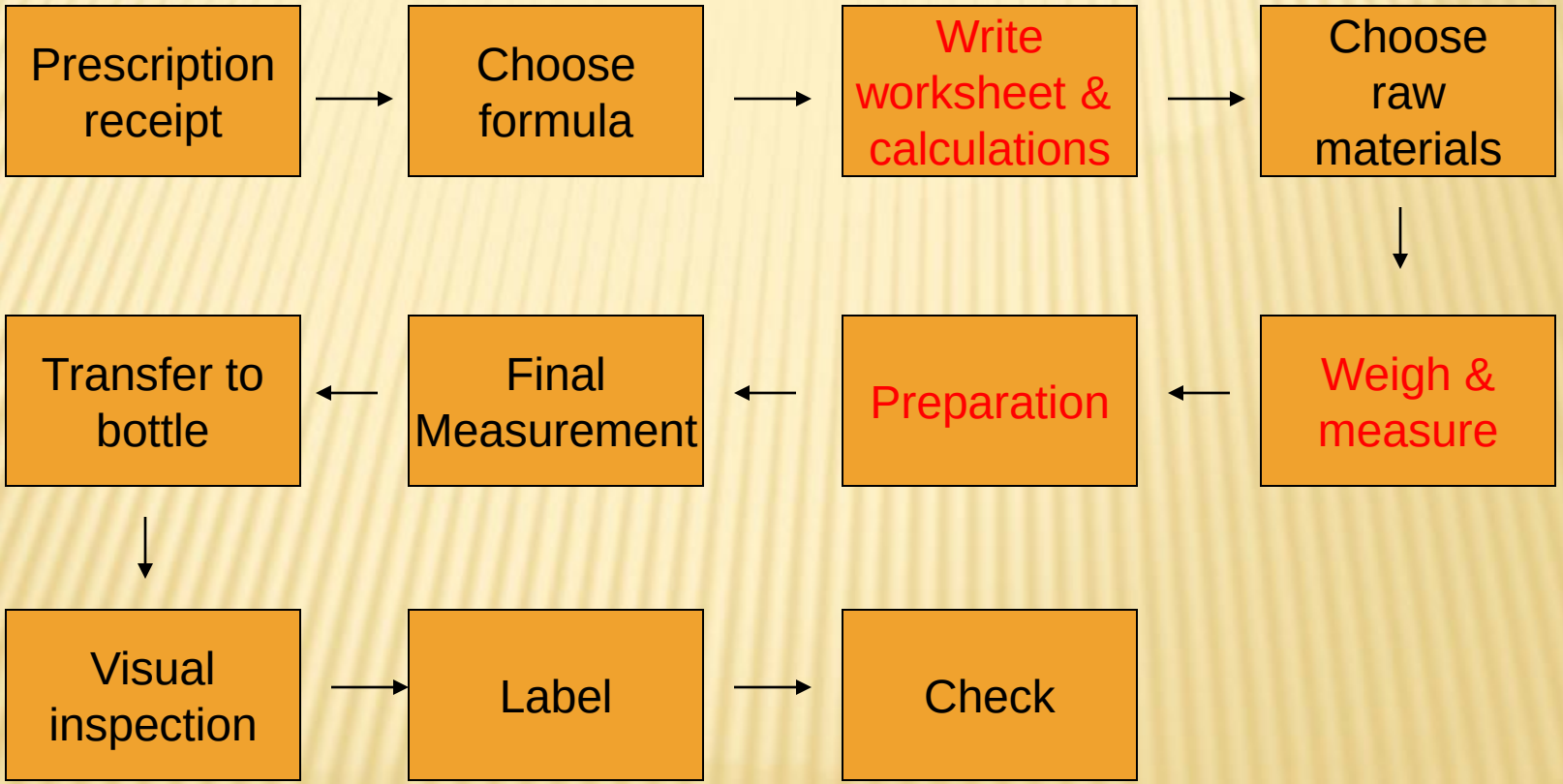
PROCESS MAP



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RISK SCORING

Risk = S x O x D

- E.g. Calculations
  - 5 x 1 x 5 = 25
- E.g Weigh/measure
  - 5 x 3 x 1.5 = 22.5
- E.g Preparation
  - 1 x 1 x 5 = 5

Acceptable risk score – depends on the patient (consider risk of NOT preparing)

RISK REDUCTION MEASURES

- Testing of raw materials
- Master worksheets
- One strength only
- Training packages
- Simple formulae
- Short shelf-life

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VALIDATION MASTER PLAN

- Staff
  - Documented training plans (qualification)
  - Continuing education
  - Examination every year (revalidation)
- Process
  - Dose concentration, particle size for oral liquids (outsource to laboratory)
  - Cross-contamination check (outsource)
  - Microbiological control
- Cleaning
  - Cross-contamination check (outsource)
  - Cleaning records
- Equipment
  - Verification of balance
  - Ventilation system (outsource)
  - Temperature & humidity monitoring system

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POLICY ON PRODUCT DEVELOPMENT

- Scope - development of products for individual patients, including children (with possible expansion of use in time)
- Pharmacotherapeutic rationale (e.g. are other ACEi's available?)
- Facilities for making small scale products only (Magistral and officinal preparations)

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PROCUREMENT

- Raw materials – powder if available (tablets if powder not available), suspending agent
- Packaging materials – amber glass bottle with child-resistant plastic screw top, labels
- Equipment – pestle & mortar, balance, laboratory materials, magnetic mixer

LOGISTICS

- Request from the ward
  - Dispensing according to a prescription for an individual patient
- Preparation on Pharmacy
- Fridge storage (2 to 8 degrees)
- Lead time – 2-3 hours
- Delivered for patient
- Short shelf-life

ISSUES FOR PRICING

- Cost of captopril & ora-sweet/ora-plus (or syrup)
- Packaging – bottles, tops, labels, outer bag, oral syringes
- Consumables used in preparation
- Lighting, heating, air handling unit
- Personnel costs (including training)
- Frequency and number of preparation

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SUMMARY

- The preparation of extemporaneous products are the highest risk area of pharmacy practice. But there is a clinical need.
- So our mission should be with minimal risk to do:

"Right medicine, right patient, right time"

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