

Warfarin suspension  
200mcg/ml

Group B Presentation

# Group B - members

- Lene, Denmark
- Nihal, Turkey
- Jaldaz, FYROM,
- Mark, UK
- Matjaz, Slovenia
- Vincentas, Lithuania
- Juraj, Slovakia

# Our Business

- Provide service to a 200 bed childrens hospital.
- Pharmacy based facility
- Small scale non sterile preparation.
- Preparation for individual patients
- Type of products – oral liquids, creams, ointments, rectal preparations, capsules

# Our Facility

- Dedicated facility
- Two “clean rooms”
- Unclassified
- Clean room class fixtures and fittings
- Maintenance of facility and equipment sub contracted against contract
- Sanitation & cleaning by own staff against approved schedule and procedures

# Our Team

- 3 pharmacists, 4 technicians
- Head of pharmacy
- Production manager
- Quality Assurance manager

# Our Quality Management system

- Documentation
- Preparation
- Quality Control
- Contractors/suppliers
- Distribution
- Complaints & recall
- Self inspection

# Business Plan

- All medicines prepared within the pharmacy
- Not allowed to purchase or sell from/to other hospitals
- Must prepare entire range for own hospital
- Trends – rationalization of therapy and treatment
- Standard preparations vs bespoke products
- Increased patient safety – on going pharmacovigilance & evidence based therapy
- Only alternative – ward preparation. High Risk
- No external competitors
- Need new dedicated non sterile preparation facility

# Business Plan - Finance

- Building & equipment costs
- Validation costs – facility & processes
- Risk management benefits – improved patient safety
- Product costing model based on single product preparation.
- Forecast 5000 non sterile units per annum.  
Pricing structure based on overheads and raw materials
- Staff, maintenance, monitoring, validation, consumables



# Product Development Policy

- Demand – request for warfarin oral liquid
- Risk Assessment – pharmacotherapeutic aspects, evidence based approach.
- Technological aspects
- Approval/reject
- Feedback

# Risk Based Approach

- Clarify clinical need - Consider alternatives
- Therapeutic Substitution e.g. licensed equivalents
- Procurement options e.g. imports
- Practical options – crushing/dissolving solid dose forms
- Other routes e.g. rectal, injectables
- Other formulation orally e.g injection

# Risk Based Approach - warfarin

- Therapeutic need – children, elderly, difficult to swallow (NG tube)
- Licensed products not available as liquids or appropriate strength
- Balance of risk – preparation risks, therapeutic risks, risk of not treating.
- Clinical need established

# Product Risk Assessment

- Do we have a valid formula – evidence based
- Supportive stability data
- Source of raw materials
- Validated processes
- Suitable facilities
- Trained personnel
- Quality system & regulation

# Warfarin Oral Liquid 200mcg/ml

- Evaluate drug – narrow therapeutic index. High risk potential of patient morbidity if formulation fails.
- Review available data – formulations and supportive stability data
- Feasibility study
  - Evaluate preparation method. Grinding vs dissolution technique
- Raw materials
  - Tablets or powder
  - Commercially available suspending agent orasweet/oraplus preserved
- Packaging – unit dose or bottle. Considered dose uniformity issues.
- Critical stage analysis – SOD

# Warfarin

- Tablets as sodium salt
- Licensed starting materials with proven bioavailability
- Evaluate effect of manipulating dose form - grinding
- Limited solubility 1 mg/ml as salt, but 0.004 mg/ml as free base, therefore pH dependant
- pKa 5
- pH of suspending agent = 4-6
- Therefore likely to have free base and salt in formulation
- Suspend due to both solubility issues and presence of excipients in formulation which may bind drug
- Uniformity of dose ensured if effectively suspended & shake before use

# Product Specification –Warfarin suspension 200mcg/ml

- Warfarin sodium tablets 5mg 4
- Oraplus 50ml
- Orasweet to 100ml
- Pack in 100ml type 1 glass bottle, with child resistant closure and 5ml oral syringe
- Shelf life 7 days
- Storage room temperature

# Risk Identification

- Critical point analysis
- Raw materials: tablet variation, selection error 1x1x5
- Drug: Solubility vs pH of suspending agent 1x1x1
- Formula: Documented formulation exists 5x3x5
- Preparation: 5x1x5
- Cleaning/cross contamination 5x3x3
- Equipment – Pestle & Mortar, Volumetric measure 1x1x1
- People: Training & competency assessment 5x3x5
- Packaging: bottle vs unit doses to ensure uniformity of dose 3x1x1
- Labeling – clarity of critical information and user instructions 5x1x1



# High Risk Areas

- Formulation
- Preparation
- Cleaning/cross contamination
- Staff
- Labeling

# Risk Management

- Formulation – reviewed and assessed as part of risk assessment process
- Raw Materials: licensed starting materials, systems for supplier approval and audit
- Process controls – double check at critical preparation stages :assembly of tablets, grinding to uniform particle size, volume check following mixing and making to volume.
- Validation of critical process against VMP
- Documentation approval – worksheets and labels
- Procedural barrier
- Staff training and competency assessment

# Risk Management: Design for Safety

- Dedicated facility
- Suitable size – adequate space for activities required
- Minimise risk of cross contamination
- Allow good work flow – reduce risk of cross over
- Minimize risk of errors
- Suitable environmental conditions – temperature, humidity to allow safe and comfortable preparation & limit product degradation
- Easy to clean
- Clothing – coat, hat, gloves ,mask (depending on type of product and hazard ), Shoes/overshoes
- Weighing area – reduce vibration and draughts
- Type of product – assess risk of hazard & exposure to staff
- Local containment– hazardous substances e.g. dusts, volatile substances

# Validation Master Plan

- Facility
- Equipment
- Processes
- Cleaning
- Staff
- Procedures & documentation
- Change control

# Quality Control & Monitoring

- Supplier Approval – Audit, questionnaire, documentation assessment (CofA, licence, specification).
- Starting materials – if licensed quality assured, otherwise identification test if from approved supplier. Glass bottles and closures from approved supplier.
- Monitoring – facility & equipment. Monthly settle plates – trend analysis only. No limits. Used to identify changes in practice. Water sources, sinks & drains.
- Cleaning validation – reduce cross contamination risk. Cleaning staff competency assessment, Chemical residue testing.
- Staff competency assessment – annually (re-training, observation, simulation).
- Process validation
- End product testing – programme of chemical analysis (external laboratory)
- Self inspection against hospital professional standards - annually
- External audit – specialist every 2 years.

# Summary

- Risk based approach
- Established clinical need
- No procurement options
- High risk product
- Reduced technical risks using simple approach to formulation and preparation
- Close liaison required with clinical colleagues to monitor effectiveness of formulation to ensure patient safety
- On going review & pharmacovigilance

- Applause please
- No questions