ESTABLISHING A CENTRALISED STERILE COMPOUNDING SERVICE

National Pharmacy Programme Management Office

Introduction

The National Pharmacy Strategy (NPS) is a 10-year plan to transform the delivery of pharmaceutical care and medication management in Singapore that was approved by the Ministry of Health (MOH).

In 2017, MOH approved the implementation of the Hub-and-Spoke compounding and distribution model to provide centralised sterile drug compounding service in the Singapore public healthcare sector. Establishing a centralised sterile compounding service is an initiative under the NPS Thrust 3, Re-design Supply Chain.

The National Pharmacy Strategy

Objectives

- ❑ Maximise economic benefits by leveraging on technology / robotics to address key concerns such as medication and staff safety, productivity, shrinking local workforce, quality assurance and evolving models of care
- ❑ Strengthen the public healthcare sector's system-level resilience to achieve continual supply of sterile compounded drug products

Method

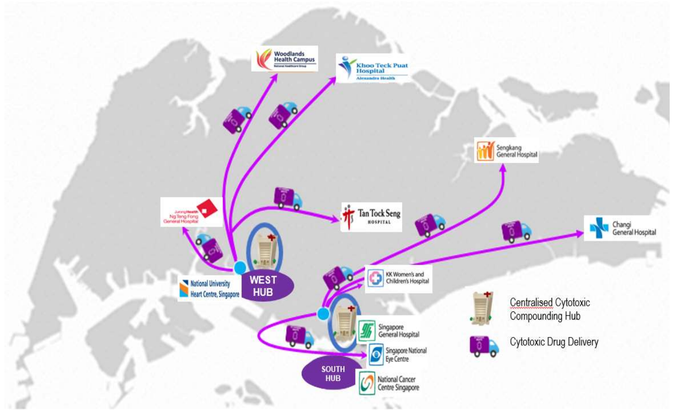
Hub-and-Spoke Sterile Drug Compounding Model

A total of three non-cytotoxic (Fig. 1) and two cytotoxic hubs (Fig. 2) are proposed to cater to the needs of public healthcare institution. The hubs will be developed to Good Manufacturing Practice (GMP) standards to protect the interests of patients, reduce the level of risk inherent in large-scale production of drugs and achieve consistent high quality manufacturing standards.

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP standards is an internationally recognised quality assurance system in drug manufacturing to ensure the quality of drug products.

Fig. 1: Proposed three non-cytotoxic hubs

Fig. 2: Proposed two cytotoxic hubs



Risk Assessment

Sterile drug compounding is a known high risk activity. Failure Mode Effect Analysis (FMEA) has been undertaken to determine potential points of failure to the sterile compounding process and to identify possible measures to prevent/mitigate these failures. Table 1 shows the possible failure modes in the sterile compounding process and the risk priority number assigned. The continuous risk assessment approach is central to the principles of GMP.

Competency Building

In parallel, to build competency in sterile compounding, a Centralised Drug Compounding Workgroup was formed in 2017, helmed by the Chief Pharmacist of Singapore. This workgroup has also been working on the harmonisation of various components of sterile drug compounding (Fig. 3).

Fig. 3: Functions of the Centralised Drug Compounding Workgroup

Develop list of products to be compounded by hubs, service level agreements	Harmonise formulae & standard operating procedures	Develop national training programme – Pharmaceutical Society of Singapore Sterile Compounding Programme	Discuss and flag practice issues, serve as expert panel to Governance Committee

Table 1: Application of FMEA in the sterile compounding process

Processes & Sub processes	Current Practice	Failure Modes	Proximate Causes	Effects (Negative impact on patient safety)	Severity	Probability	Likelihood of Detection	Risk Priority Number
1. Handling of starting materials	• Drugs/ infusion solutions are received by compounding lab and used with assumption that registered products meet quality standards • Items are picked according to order without explicit requirement to inspect material	• Specifications (e.g. formulation and tolerance limits) may have been changed by the manufacturer • Inconsistent quality such as batch to batch variability • Material defects not detected by staff	• Specifications changed without notification to users • No robust routine verification of incoming material quality • No requirement for systematic check of starting materials. • No requirement to document checks	• Inconsistent quality of compounded sterile preparations (CSP): potency and sterility affected	5	1	5	25
2. Selection and handling of packaging materials	• Packaging materials (e.g. final containers for products, over pouches for light protection) of final product are ordered from supplier based on historical practice	• Quality of packaging materials may vary from batch to batch • Packaging materials may be changed without proper authorization	• No requirement to control packaging material or establish specifications for packaging material	• Inconsistent packaging materials may affect quality of final products, e.g. compromised container integrity may affect sterility and stability of final product, substandard over pouches may compromise light protection and hence stability	5	2	5	50
3. Documentation control	• Procedures are reviewed/revised as per institutional practice • Varying degrees of documentation control/ change control	• Procedures may be changed without established authorization process • Inadequate version control • Poor documentation practices e.g. erasable records, use of liquid paper	• No guidance for documentation control befitting manufacturing at institutional level • No emphasis on traceability • Lack of change control	• Superseded versions of protocols/procedure may still be in circulation and cause errors in production procedures • Inconsistent/poor in-process documentation practices hamper investigations into faulty / substandard final products	5	3	3	45
4. Management of outsourced services/ subcontractors	• Services procured based on best price and fulfilment of specifications e.g. laundry and sterilization services, outsourced microbiology	• Specifications of the service may change by provider without notification or agreement	• Lack of control over service providers. • Lack active monitoring service quality of service providers	• Substandard services (particularly services involving sterilization) will negatively compromise quality of final CSPs	5	1	5	25
5. Validation of aseptic technique/ processes	• Validation of operator aseptic technique or aseptic processes are conducted as per institutional requirements (if any) *(validation is a "stress test" that serves to proof that compounded products made are sterile even when compounded under worst-case-scenarios (e.g. when there are more than the usual number of people in the cleanroom (increased contaminants), or when the compounding session has been particularly long and operators are fatigued)*	• Varying standards of validation protocols • No validation of operators/ processes	• Sterile compounding facilities are not required to conduct operator or process validations • Lack guidance on how validation should be performed and how to interpret results	• No objective indication that CSPs made are sterile when compounding activities are carried out under worst-case-scenarios	5	3	5	75
6. In-process controls/ monitoring	• In-process controls/ monitoring applied as per institutional requirements (if any), e.g. *particle count monitoring during compounding session, swab of operator gloved hands, work counter top and settle plates at end of session)*	• Varying frequencies of in-process controls/ monitoring • No in-process controls/ monitoring	• In-process controls/ monitoring not mandatory • Lack of guidance on how monitoring should be performed and how to interpret results	• No means of detecting excursions in critical parameters such as particle counts during the critical activity of sterile compounding • Efficacy of disinfection compromised • No surveillance: contaminated CSPs may be produced and distributed	5	3	5	75

Conclusion

The hub-and-spoke model will operate on a harmonised compounding workflow, leverage on technology, a well-trained work force and a reliable and efficient distribution network. The harmonised workflow and adherence to GMP standards will address the anticipated risks and identified failure modes to improve patient and staff safety, work productivity and support new models of care. This project is the first in Southeast Asia and the success hinges on the dedication and support from the stakeholders.

A special acknowledgement to the members of the Centralised Drug Compounding Workgroup, public healthcare institutions, regulatory, infrastructure, finance groups from MOH and MOH Holdings and the Pharmaceutical Society of Singapore for their contribution to this national initiative.

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https://www.moh.gov.sg/hpp/pharmacists/national-pharmacy-strategy

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