National Pharmaceutical Control Bureau
MINISTRY OF HEALTH MALAYSIA

WHO Collaborating Centre for Regulatory Control of Pharmaceuticals

Member of Pharmaceutical Inspection Co-operation Scheme

Certified to ISO 9001:2008
Cert. No.: AR 2293

MS ISO/IEC 17025:2005
Certified to MS ISO/IEC:17025:2005
NO: SAMM 450

COLD CHAIN INSPECTION: REGULATORY PERSPECTIVE ON CURRENT STRATEGIES AND FUTURE DEMANDS

Muhammad Lukmani Ibrahim
Deputy Director| Centre for Compliance and Licensing
National Pharmaceutical Control Bureau
Ministry of Health Malaysia

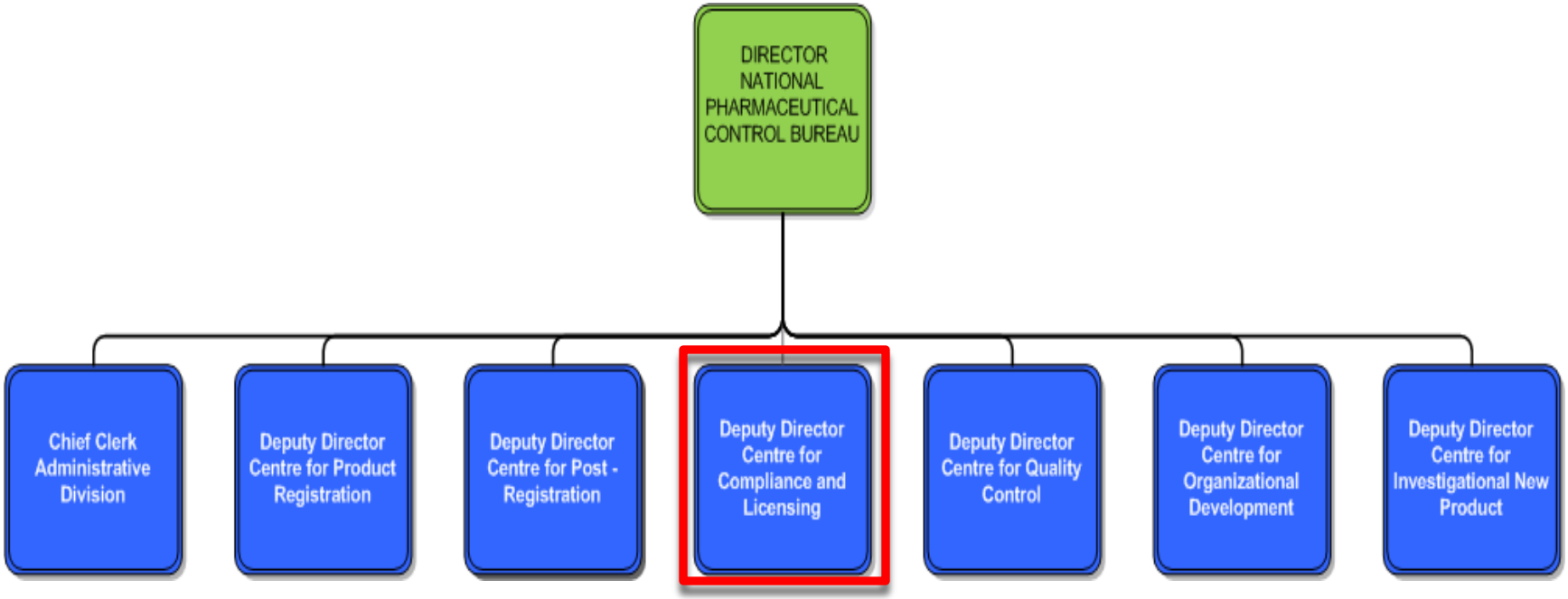
Tel: +603-78835564| Fax: +603-79571200
Website: www.bpfk.gov.my | Email: lukmani@bpfk.gov.my

Content

- Introduction
- Background
- Definition
- Regulator Requirements
- Cold Chain Inspection
- Current Senario
- Way Forward

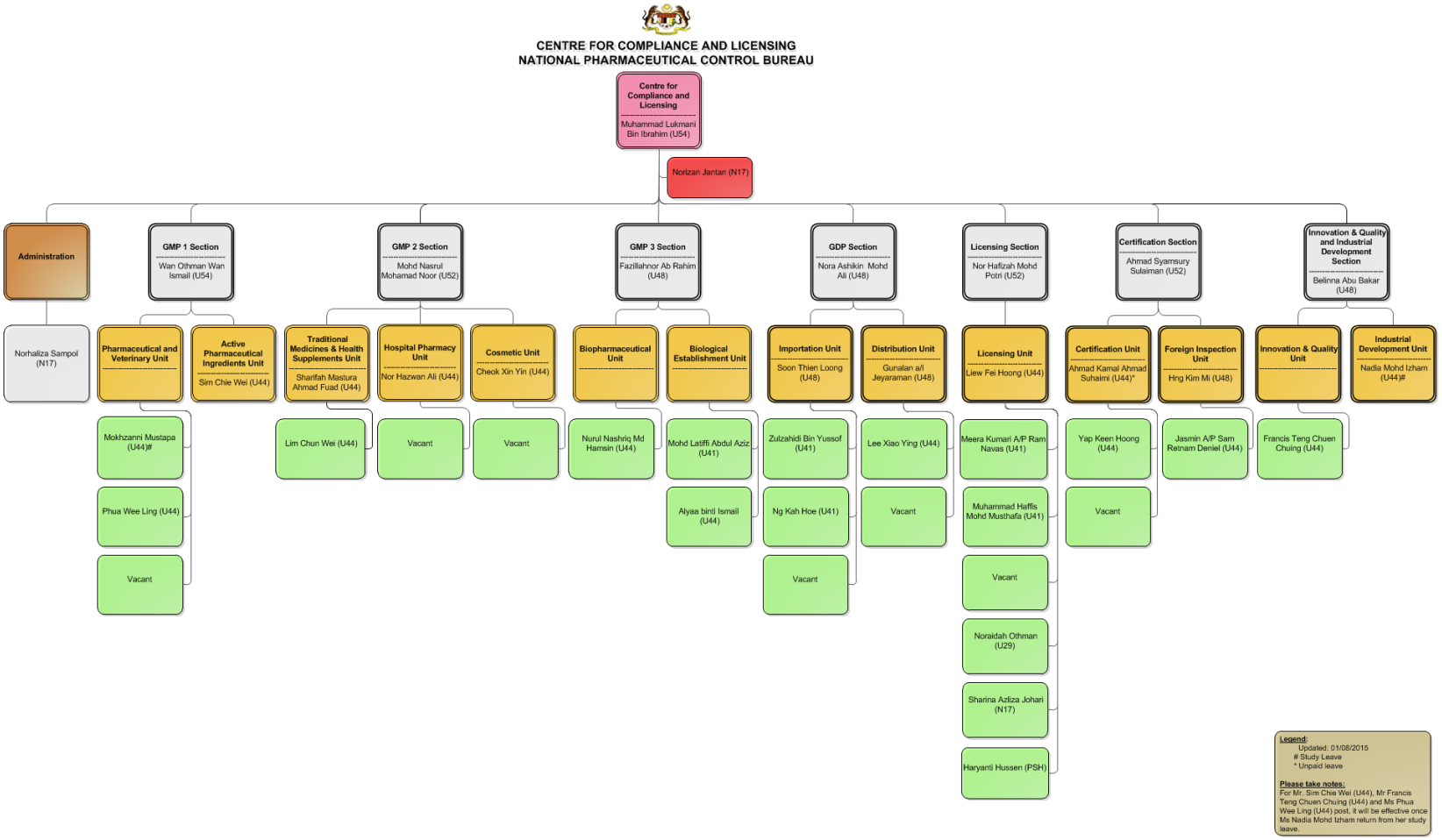
Introduction (1)

Organization Chart National Pharmaceutical Control Bureau (NPCB)



Introduction (2)

Organization Chart Centre for Compliance and Licensing NPCB



Background (1)

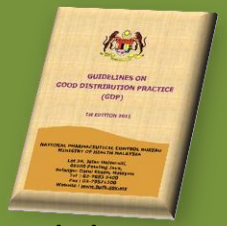
History of Good Distribution Practice (GDP)

Guidelines on Good Storage Practice (GSP)

1st Edition Jan 1995

Guidelines on Good Storage Practice (GSP)

2nd Edition 2004



Guidelines on Good Distribution Practice (GDP)

1st Edition 2011

Guidelines on Good Distribution Practice (GDP)

2nd Edition 2013

(Dual language)

Background (2)

Guidelines on Good Storage Practice (GSP)
1st Edition 1995

QUALITY STORE MANAGEMENT

PART ONE

Personnel

Premises & Facilities

Stock handling & Stock Control

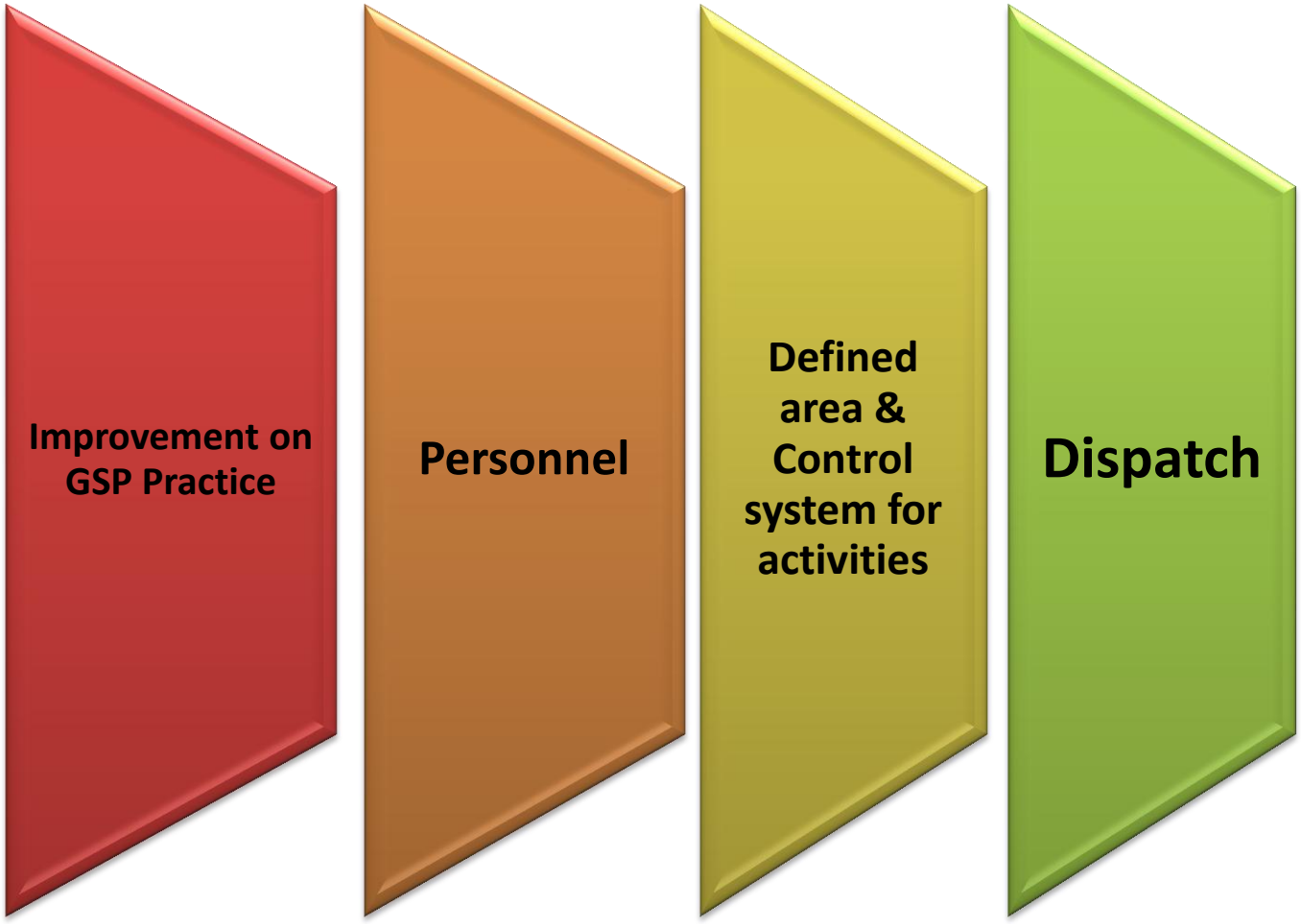
Disposal of pharmaceutical products

Documentation

PART TWO

- Product Complaints
- Product Recall

Background (3)

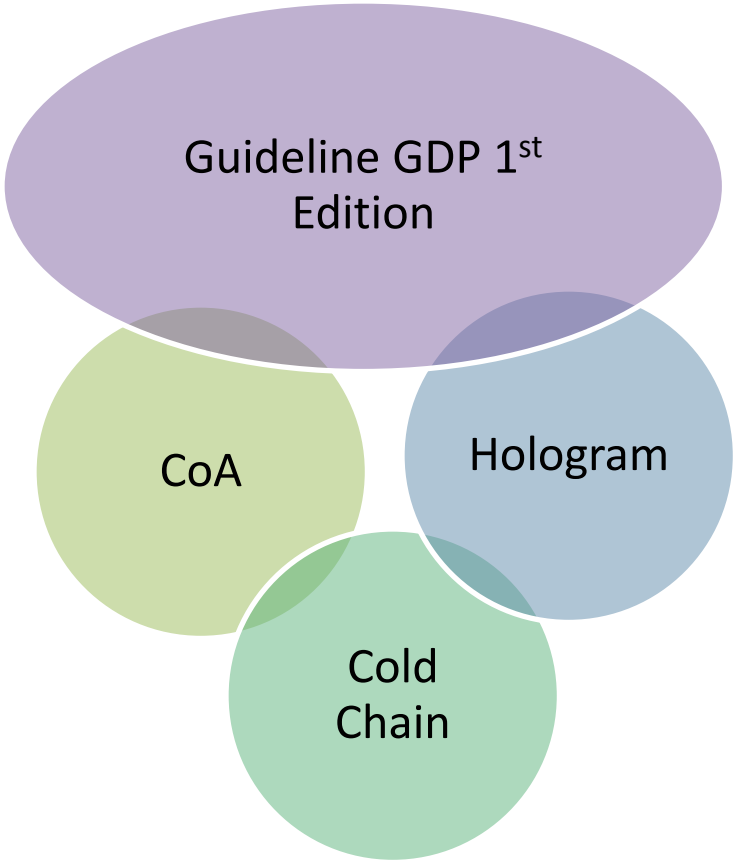


Guidelines on Good Storage Practice (GSP) 2nd Edition 2004

Background (4)

Guidelines on Good Distribution Practice (GDP)
1st Edition 2011

Background (5)



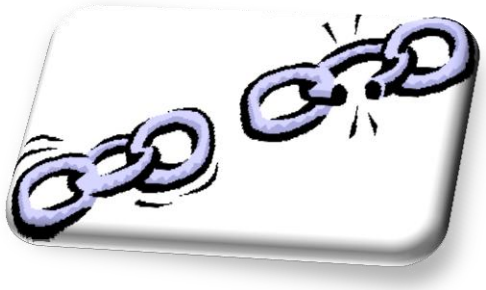
Guidelines on Good Distribution Practice (GDP) 2nd Edition 2013 (Malay & English Version)

Vaccine Lot Release (VLR) in Malaysia

- Review of Lot Summary Protocol (LSP)
- **Cold chain Inspection (CCI)** – comprises of Physical Checking & Temperature Monitoring
- Evaluation of LSP + CCI satisfactory = Issuance of Lot Release Certificate (LRC)
- Evaluation of LSP and/or CCI not satisfactory = Issuance of Notification of Non Conformance (NNC)

Definition (1)

- **COLD CHAIN** - The process used to maintain optimal conditions during the transport, storage, and handling of cold chain products, from the point of manufacturer to the point of use.



Definition (2)

- **TEMPERATURE EXCURSION** - An excursion event in which a time- and temperature-sensitive products is exposed to temperatures outside the range(s) prescribed for storage and/or transport. These temperature range may be the same or different which are determined by the manufacturer, based on stability data

Directives (1)

Directives Good Distribution Practice (GDP)

Issued by Senior Director of Pharmaceutical Service Division

Directive under Regulation 29 Control of Drugs and Cosmetics Regulation 1984

No.1/2011

- Compliance towards Good Distribution Practice (GDP) Guideline requirements
- Enforced since 1st January 2012
- For all local manufacturers/ importers/ wholesalers of registered products/ notified cosmetic
- Inclusive of Chapter 15 (Management of Cold Chain Products/ Materials) – Guidelines on GDP Second Edition 2013

Requirements (1)

Chapter 15 of Guidelines on GDP Second Edition 2013

- Main points:
  - Qualification & validation of storage facility (15.3)
  - SOPs for receiving & storage (15.5), distribution(15.4), packing(15.15 & 15.16), out-of-specification (15.23)
  - Temperature mapping, monitoring, record (15.8-15.10)

Requirements (2)

- Maintenance of equipment (air conditioning system, refrigerator) (15.11) and calibration (temperature monitoring devices) (15.14)
- Alarm system (15.12)
- Alternative power system/ area (15.13)
- Transportation (15.19-15.22)

Directive (2)

Directives on Vaccine Lot Release (VLR)

Issued by Senior Director of Pharmaceutical Service Division

Directive under Regulation 29 Control of Drugs and Cosmetics Regulation 1984

No.16/2014

- Effective 1st February 2015
- Implementation of Vaccine Lot Release on All Registered Vaccine Product Imported to Malaysia
- For all product registration holder (PRH), Importers and Wholesalers registered vaccine

Reference Guidelines (1)

"Storage condition for medicinal products should be maintained during transportation within the defined limits as described on the outer packaging and/or relevant packaging information."

PIC/S Guide to GDP for Medicinal Products (Chapter 9)

"Short term temperature excursion is allowed provided satisfactory stability data and scientific and technical justification by the manufacturer."

(USP General Chapter <1079> & WHO Model Guidance for the Storage and Transport of Time- and Temperature-sensitive Pharmaceutical Products Annex 9 No.961, 2011)

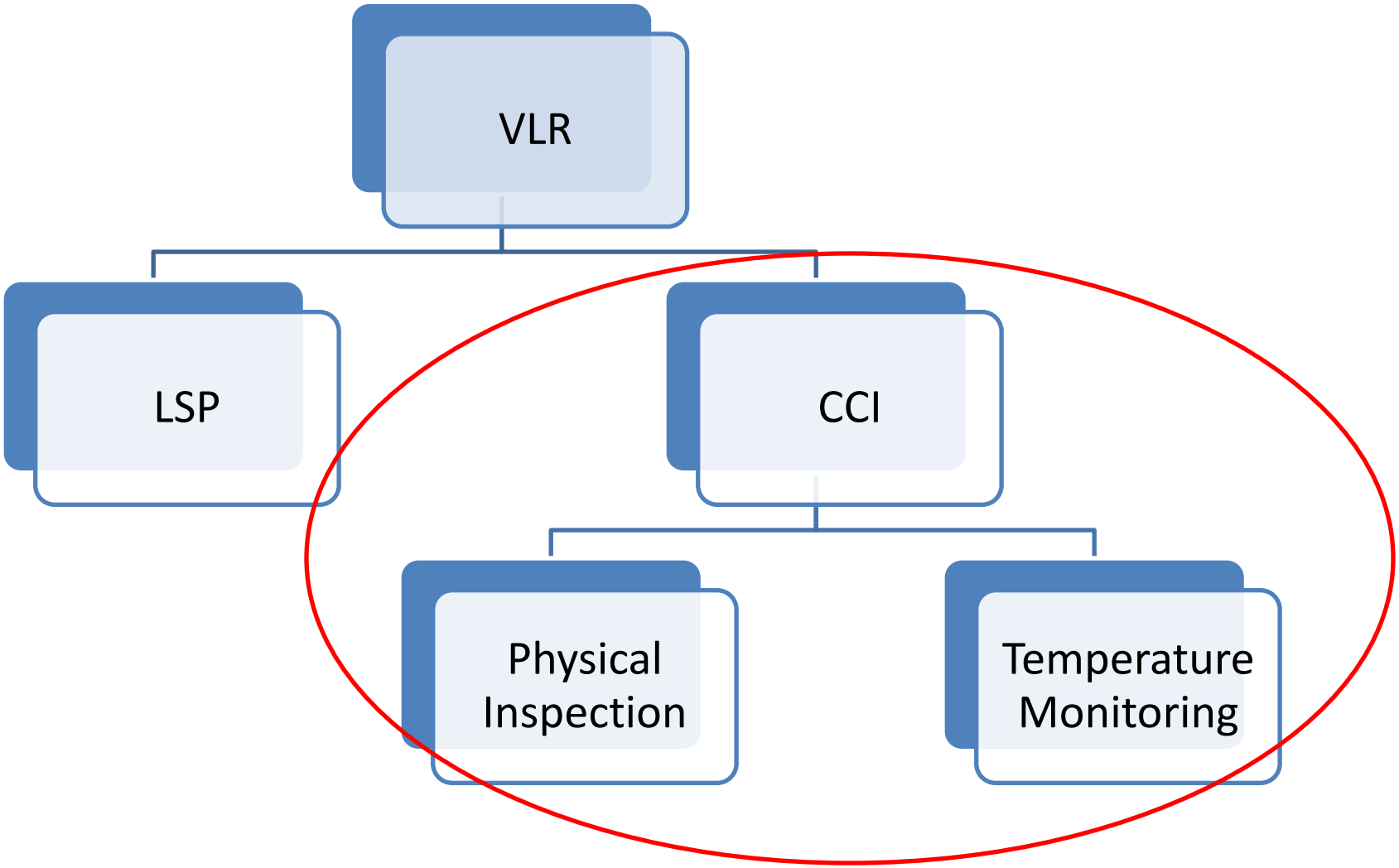
Reference Guidelines (2)

WHO Classification and Temperature Criteria for International Shipment of Vaccines (for at least 48 hours)[#]

Class	Type of vaccine	Ambient temperature	Minimum temperature allowed	Maximum temperature allowed
A	OPV	+43°C	no limit	+8°C
B	BCG Hib (freeze-dried) measles MR MMR meningococcal A&C yellow fever	+43°C	no limit	+30°C
C	DTP DTP–HepB DTP–Hib (liquid) DT	+43°C	+2°C	+30°C
	IPV HepB Hib (liquid) Td TT	-5°C	+2°C	+30°C

[#] Guideline on the International Packaging and Shipping of Vaccine (WHO/IVB/05.23)

Cold Chain Inspection (CCI)



Physical Inspection (1)

Name and Dosage

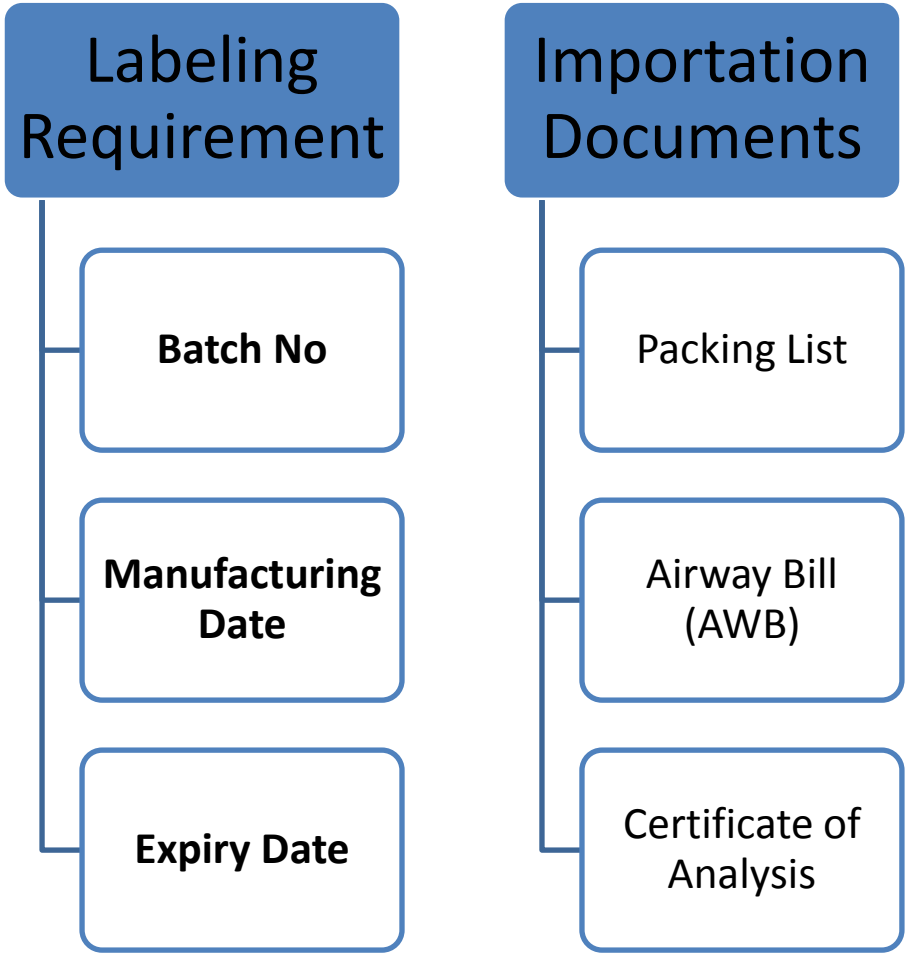
Quantity

Name and Address of Manufacturer

Condition of Outer Package

Seal of Package

Physical Inspection (2)

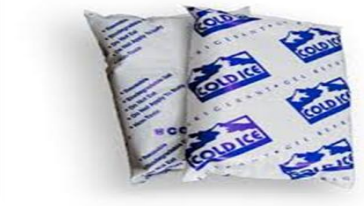


Temperature Monitoring (1)

Type of Coolant Used

- Dry Ice

- Ice Pack



- Phase Change Material (PCM)

Temperature Monitoring (2)

Temperature Monitoring Devices Used:

Temptale4

Vax Alert

Q Tag 2+

Freeze tag

Q Tag CLm Doc

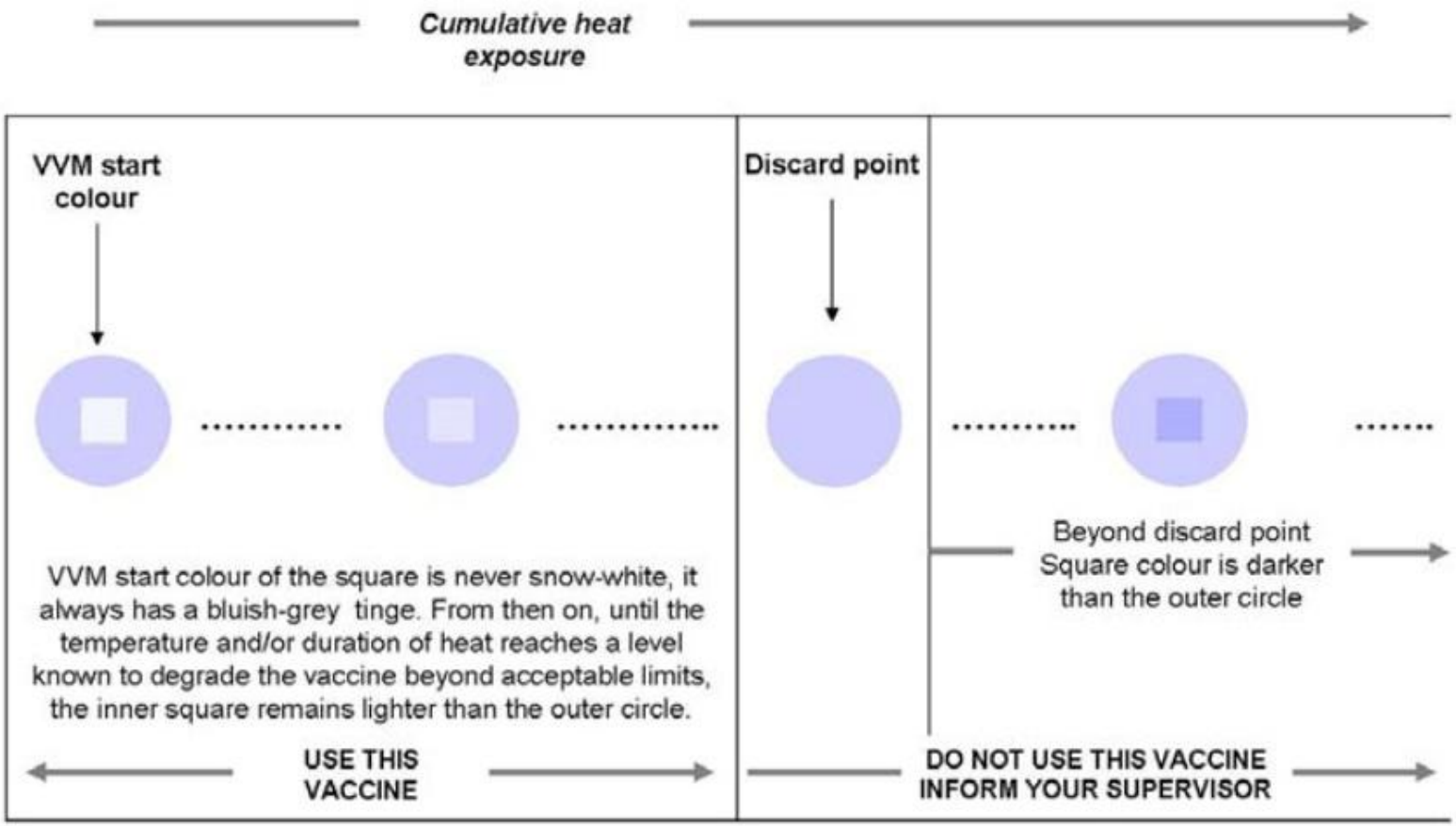
Warm Mark Duo CCM/ 3M CCM Card

Vaccine Vial Monitor (VVM)

Symbol	Explanation	Stage
	The inner square is lighter than the outer circle. If the expiry date has not passed, **USE** the vaccine.	I
	As time passes the inner square is still lighter than the outer circle. If the expiry date has not passed, **USE** the vaccine.	II
	**Discard point:** the color of the inner square matches that of the outer circle. **DO NOT** USE the vaccine.	III
	Beyond the discard point: inner square is darker than the outer circle. **DO NOT** USE the vaccine.	IV

From WHO (wwww.who.int).

Interpretation of VVM



VVM Reaction Rates by Category of Heat Stability

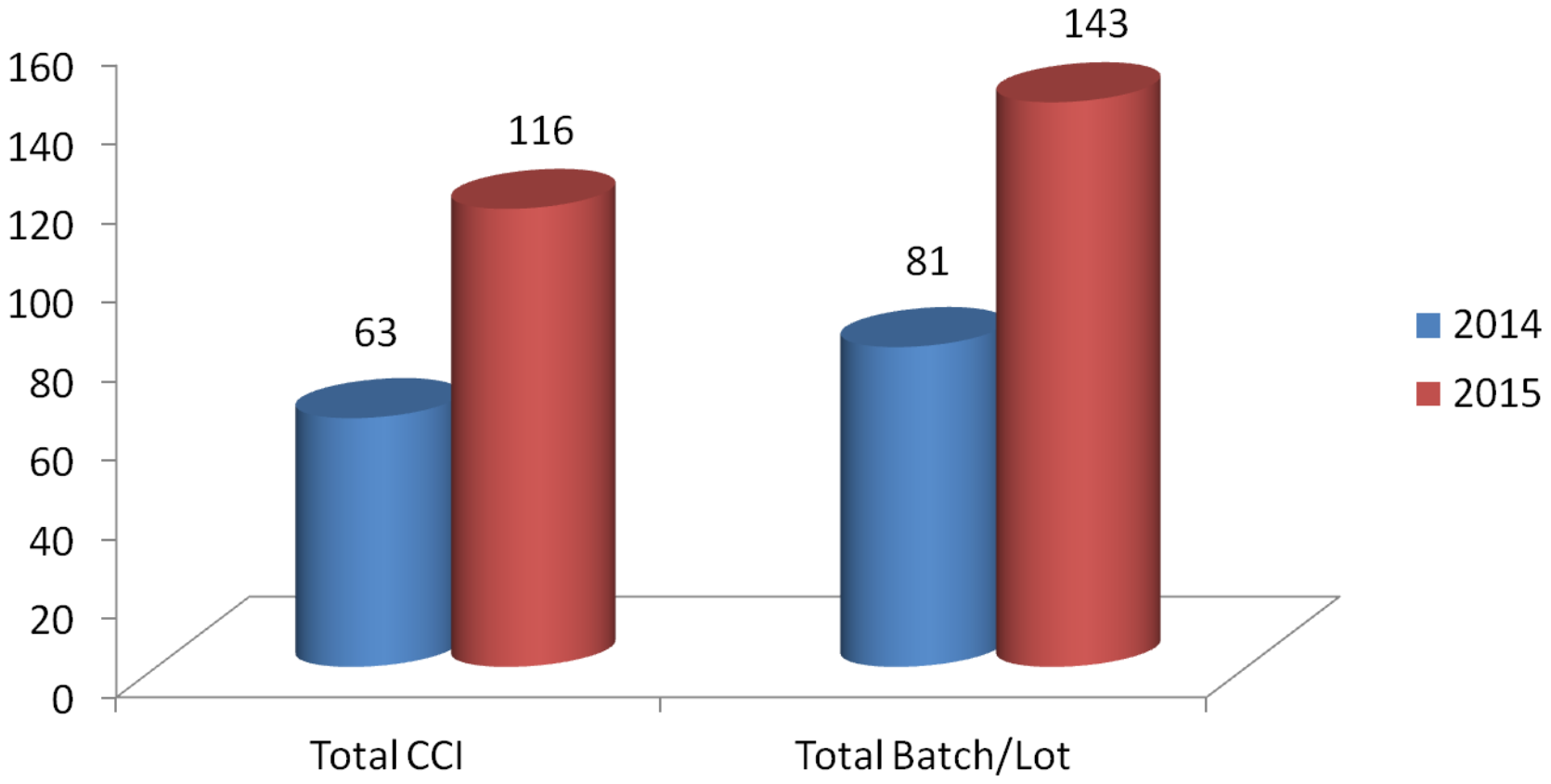
Category (Vaccine)	No. days to end point at +37°C	No. days to end point at +25°C	Time to end point at +5°C
VVM30 High Stability	30	193	> 4 years
VVM 14 Medium Stability	14	90	> 3 years
VVM 7 Moderate Stability	7	45	> 2 years
VVM2 Least Stable	2	NA*	225 days

*VVM (Arrhenius) reaction rates determined at two temperature points

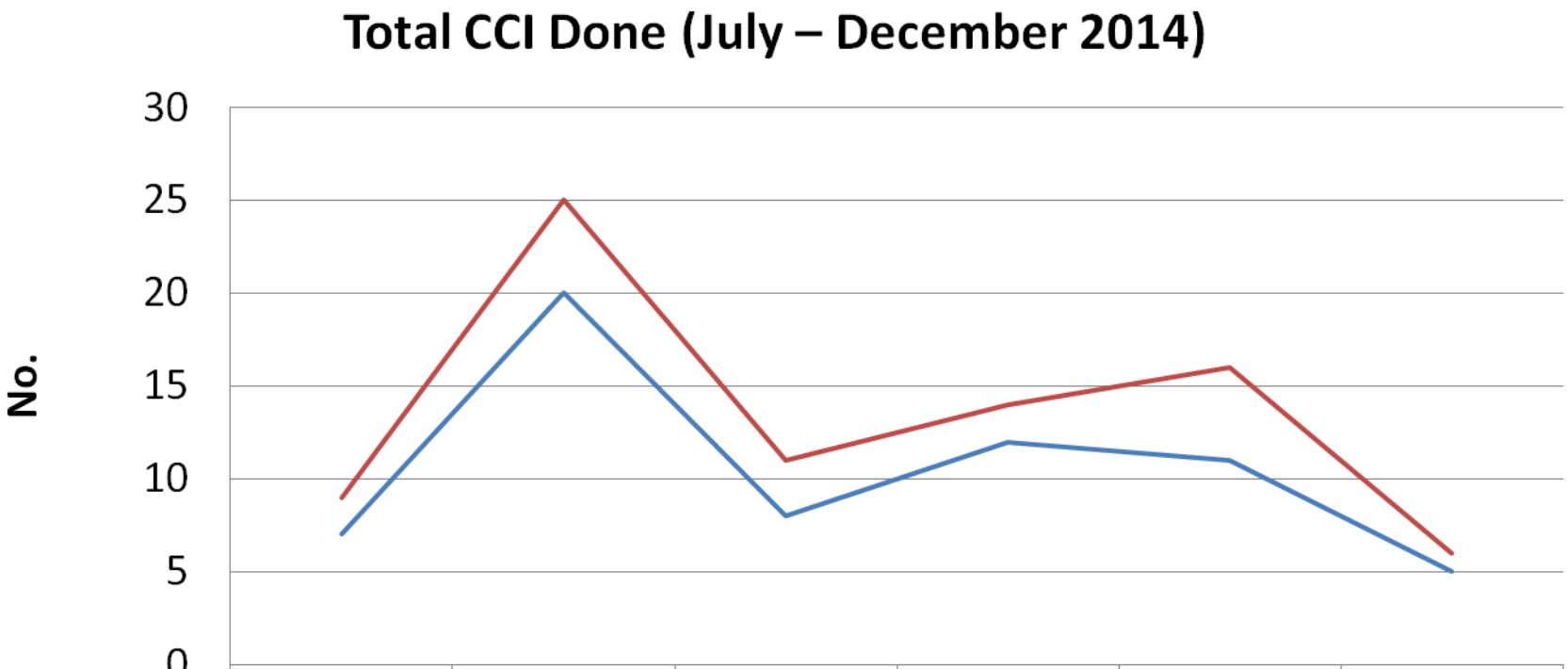
Supporting Documents (If Excursion)

- Stability Studies:
  - Real Time Stability Study (ICH)
  - Accelerated Stability Study (ICH)
  - Thermal Cycling Study
- Packaging Validation Data Report
- Shipping Validation Data Report

Statistical Data on CCI (Jul 2014-Jul 2015)

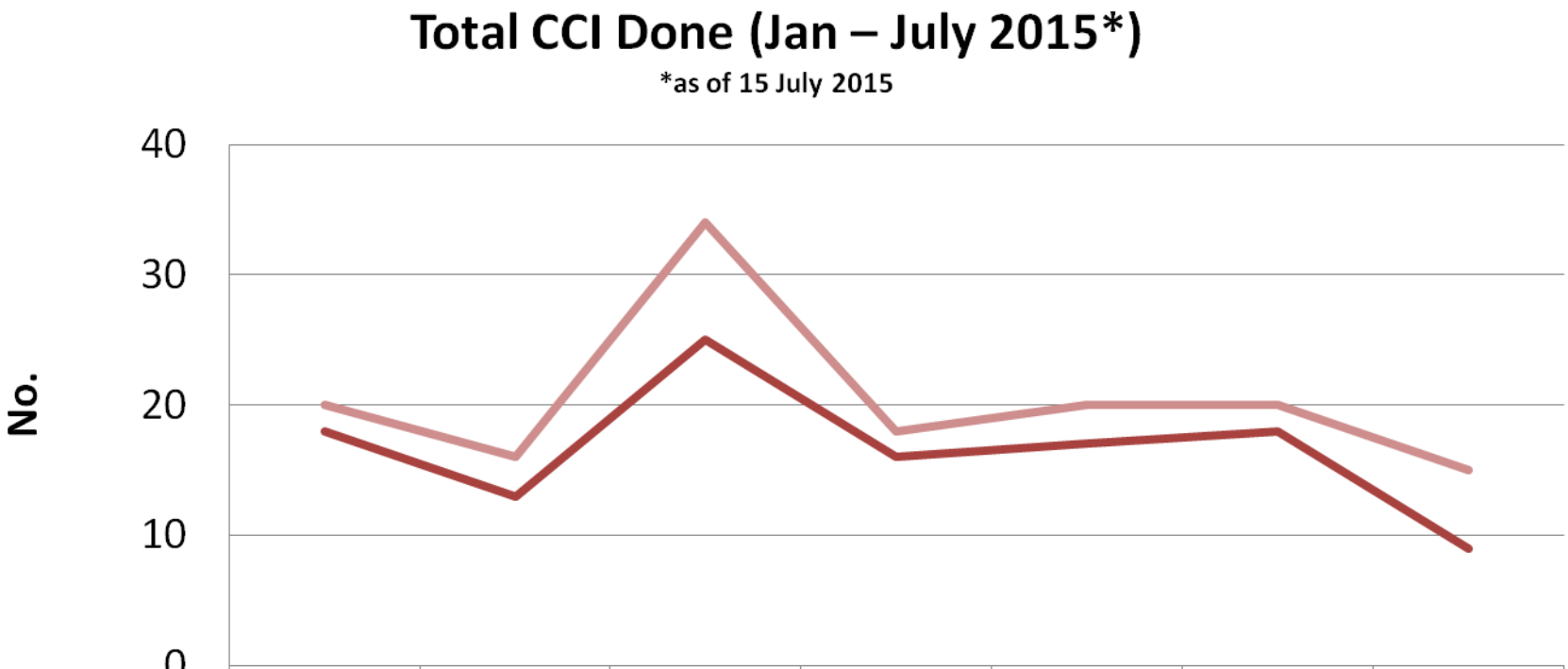


Total CCI During Pilot Study



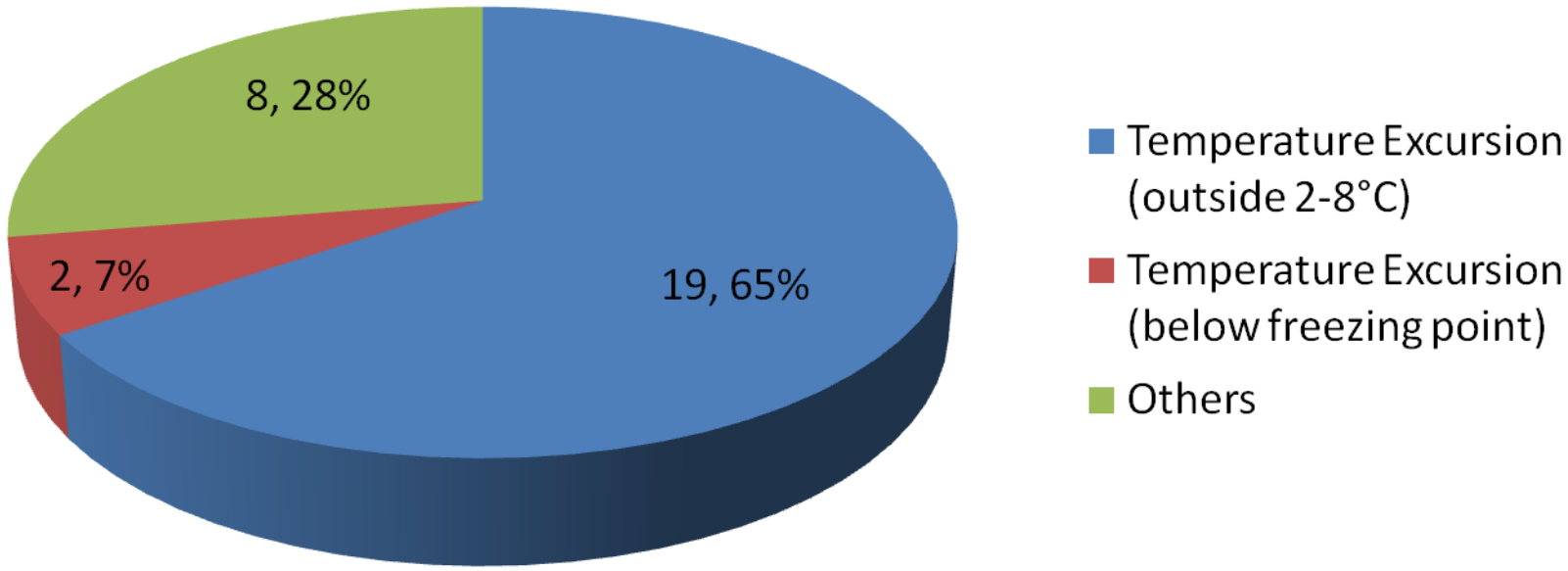
	July	Aug	Sept	Oct	Nov	Dec
Total CCI	7	20	8	12	11	5
Total Lot	9	25	11	14	16	6

Total CCI During Full Implementation



	Jan	Feb	Mar	Apr	May	June	July
Total Cci	18	13	25	16	17	18	9
Total Lot	20	16	34	18	20	20	15

Findings During Pilot Study



SHAKE TEST

- PURPOSE : To determine whether adsorbed vaccines (DPT, DT, Td, TT, Hepatitis B, Hib liquid, and/or combinations of these) have been affected by freezing.

➢ Conducted when Temperature monitoring devices indicates temperature exposure below 0 C

Shake Test (1)

Shake Test Protocol

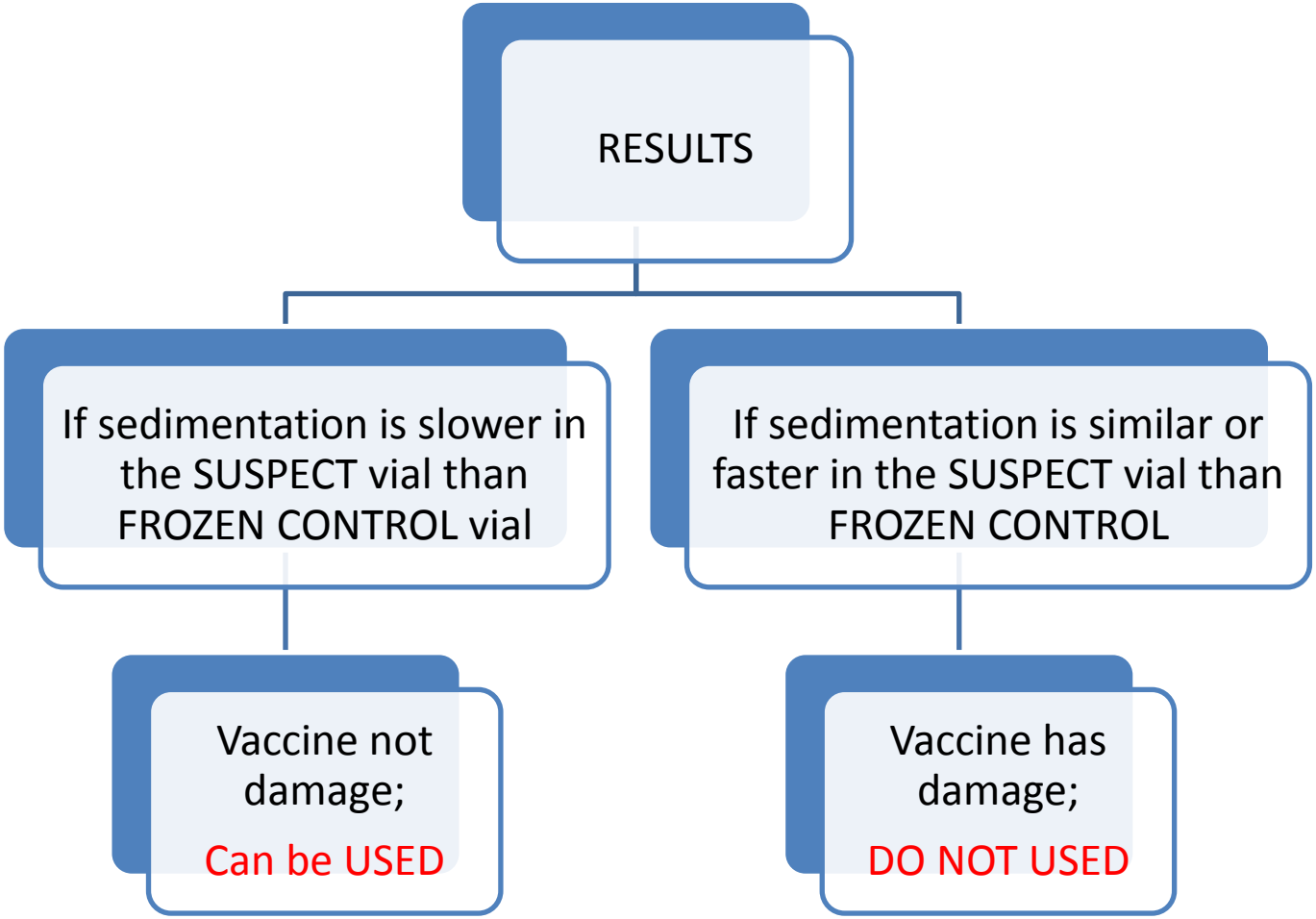
Select one vial from each type and batch of SUSPECT vaccine as CONTROL. Freeze the control vials until they are solid frozen, label them FROZEN

Allow FROZEN CONTROL vials to thaw completely

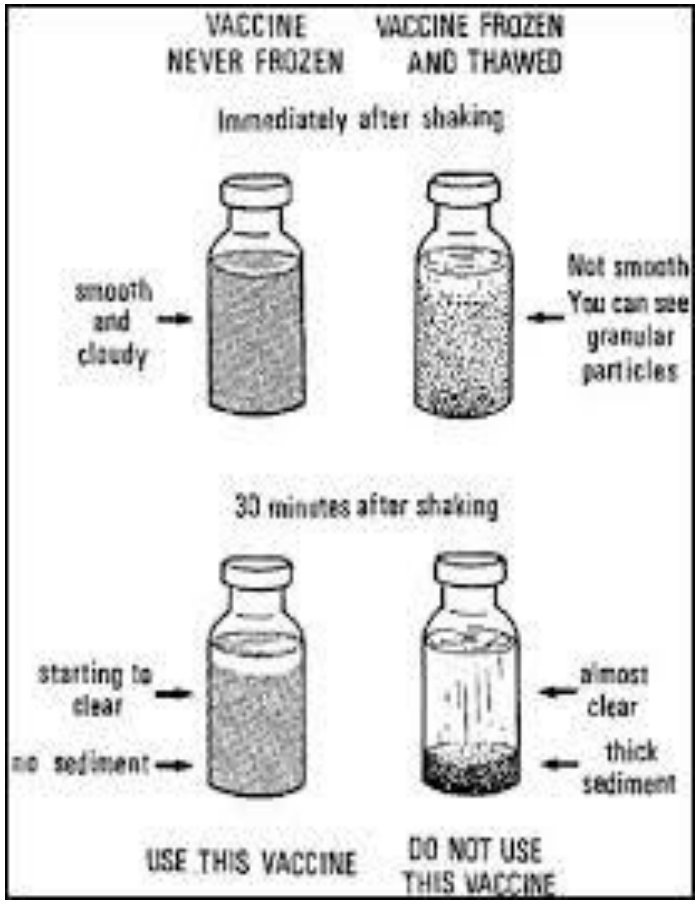
Shake FROZEN CONTROL and SUSPECT vials from the same batch together in one hand for 10-15 seconds

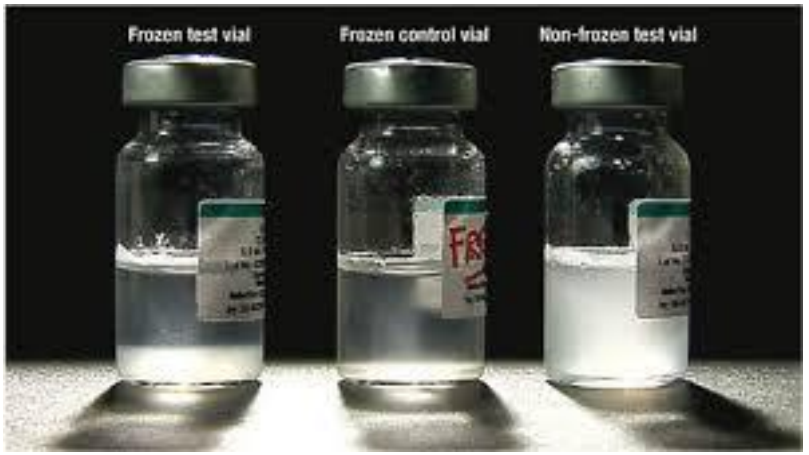
Observe FROZEN CONTROL and SUSPECT vials side-by-side to compare their sedimentation rates

Shake Test (2)


RESULTS
If sedimentation is slower in the SUSPECT vial than FROZEN CONTROL vial
If sedimentation is similar or faster in the SUSPECT vial than FROZEN CONTROL
Vaccine not damage;
Can be USED
Vaccine has damage;
DO NOT USED

Shake Test (3)


VACCINE NEVER FROZEN
VACCINE FROZEN AND THAWED
Immediately after shaking
smooth and cloudy
Not smooth You can see granular particles
30 minutes after shaking
starting to clear
no sediment
almost clear
thick sediment
USE THIS VACCINE
DO NOT USE THIS VACCINE


Frozen test vial
Frozen control vial
Non-frozen test vial

Other Requirements

- Usage of NPCB Sticker during CCI (Letter Bil(28) dlm. BPFK/30/01/12 SJ3 dated 24th October 2014)
- Requirement for PRH to submit Packaging and Shipping Validation Report (Letter Bil(16) dlm. PKK/VLR/2014 dated 11th November 2014)

Way Forward (1)

- To implement Plasma Product Lot Release (which includes LSP and CCI)
- CCI for Plasma Products – Cold chain and Non Cold Chain Items
- Target Period : Pilot study to commence in Jan 2016

Way Forward (2)

- Enhancement of GDP Requirements especially on Management of Cold Chain Products up to end users (clinics and private sector)
- ➢ Maintain quality, safety and efficacy of products
- ➢ Reduce unnecessary wastage
- Training on Handling of Cold Chain Products for end users
- ➢ Increase awareness of new requirement and knowledge

Regulator's concern..

Quality,

Safety,

Efficacy

References

- Guidance document and Guidelines for Vaccine Lot Release in Malaysia, Revised April 2015
- PIC/S Guide to Good Distribution Practice for Medicinal Products, June 2014
- Supplementary Notes on Management of Cold Chain Products/Materials, 2014
- Guidelines on Good Distribution Practice (GDP), 2nd Edition , 2013
- WHO Temperature Sensitivity of Vaccines, WHO/IVB/06.10, 2006
- WHO Guidelines on the International Packaging and Shipping of Vaccines, WHO/IVB/05.23, 2005


Thank you!

National Pharmaceutical Control Bureau

National Pharmaceutical Control Bureau
MINISTRY OF HEALTH MALAYSIA

WHO Collaborating Centre for Regulatory Control of Pharmaceuticals

Member of Pharmaceutical Inspection Co-operation Scheme

Certified to ISO 9001:2008
Cert. No.: AR 2293

Certified to MS ISO/IEC:17025:2005
NO: SAMM 450