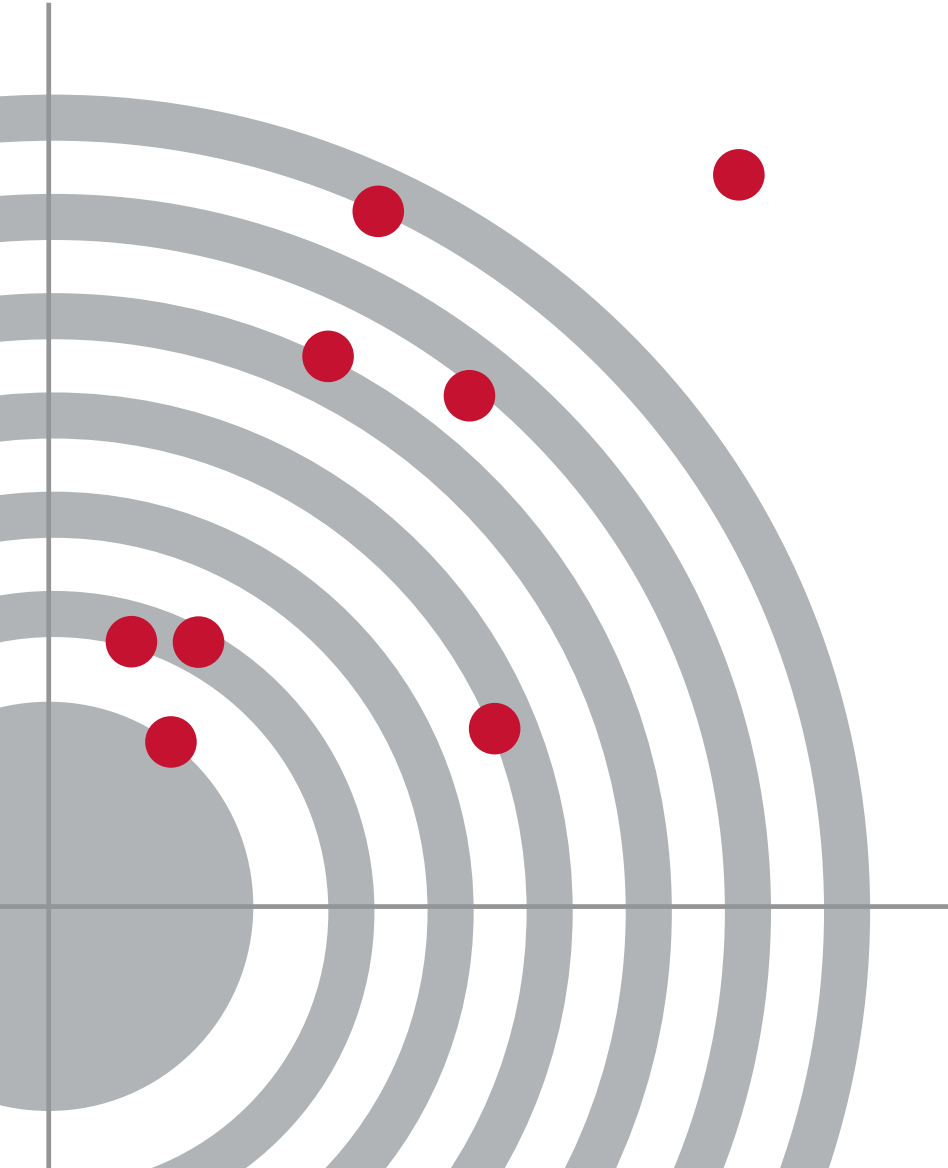


Pharmaceutical and vaccine quality

ILLUSTRATED

ÜMIT H. KARTOĞLU



EPELA 

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Pharmaceutical and vaccine quality **ILLUSTRATED**

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Geneva, Switzerland

Foreword

James Vesper, PhD, MPH
Rochester, New York
October 2015

An expert on risk management is said to have a poster on his office wall with two theorems of communication:

- Theorem 1. One-half of the world's problems are caused by people using the same word for different things.
- Theorem 2. The other half of the world's problems are caused by people using different words for the same thing.

If you have facilitated group meetings, written guidelines, or led training sessions, you probably have experienced those problems. And, if you have, this book, *Pharmaceutical and Vaccine Quality Illustrated*, will be a valuable addition to your bookshelf. Dr. Kartoğlu has researched a long list of terms important in pharmaceutical and vaccine manufacturing, distribution, and quality and provided clear definitions. He has used his skills as an illustrator and photographer to make certain terms and concepts even easier to understand. Even if you haven't experienced terminology confusion, this book is still extremely valuable as a reference tool and information source. Simply browsing through it will make you smarter.

As readers interested in public health, medicines and quality, we need to commend Dr. Kartoğlu for making this publication freely available using a creative commons license. In doing so, he has provided a valuable resource that will promote more precise and effective communication and solve at least a few of the world's problems.

Foreword

Thomas C. Reeves, Ph.D.
Professor Emeritus
The University of Georgia
October 2015

What does it take for someone to create a glossary or dictionary? It surely takes extraordinary dedication and effort. Beginning in the early 1800s, Noah Webster spent nearly two decades compiling his *American Dictionary of the English Language* containing 70,000 words and in the process taught himself twenty-eight languages to be able to comprehend and communicate the etymology of words. Sir James Murray began his editorship of the *Oxford English Dictionary* in 1879 and was still working diligently on it when he died in 1915. The 12-volume dictionary with 414,825 words was not finally published until 1928.

Now we live in the information age, a time when crowdsourcing and the semantic web might suggest that the efforts of a dedicated scholar to create a dictionary or glossary are no longer necessary. Dr. Ümit Kartoğlu's impressive *Pharmaceutical and Vaccine Quality Illustrated* clearly demonstrates that such a suggestion is premature.

From "ABC analysis" to the "Zeroth law of thermodynamics," and everything in between, this compendium of 730 technical terms accompanied by numerous compelling illustrations will prove to be an invaluable resource for professionals and practitioners concerned about the quality, purity, safety and suitability of pharmaceutical products. You don't have to be an expert in this field (and I am not one) to recognize the dedication, effort, and caring that Dr. Kartoğlu has put into this masterful work. Making this resource freely available to anyone in the world through a Creative Commons license makes the caring aspect of Dr. Kartoğlu's dedication and effort all the more evident.

Behind the pages

Ümit H. KARTOĞLU, MD, DPH

Collonge-Bellerive

October 2015

Every year I organize and run the Pharmaceutical Cold Chain Management on Wheels course, which offers an exceptional 700 km tour of a comprehensive learning journey across the quality logistics. The course brings together both experts and novices from all over the world, who learn and share their experience during a ravishing 6-day travel across Turkey. Since its first inauguration in 2004, the programme of the course has been a living concept evolving around the most critical current issues and challenges of quality logistics, which are brought to a learning discussion and moderated by a team of top experts in the field of pharmaceuticals.

A comprehensive set of learning materials is prepared every year based on the anticipated demand.

During the 2015 course a participant suggested that the learning folder should include a glossary of key terms.

This was a good idea, and as the course director, my first reaction was sending a mail to all course participants asking for the list of terms they would like to see in such a glossary. In a week I received around 50 suggested terms. Naturally, they were all cold chain related with vaccine orientation. I thought that it would be useful to expand the glossary to cover the overall quality issue around pharmaceuticals and vaccines. As a result this volume includes the definitions of 730 terms.

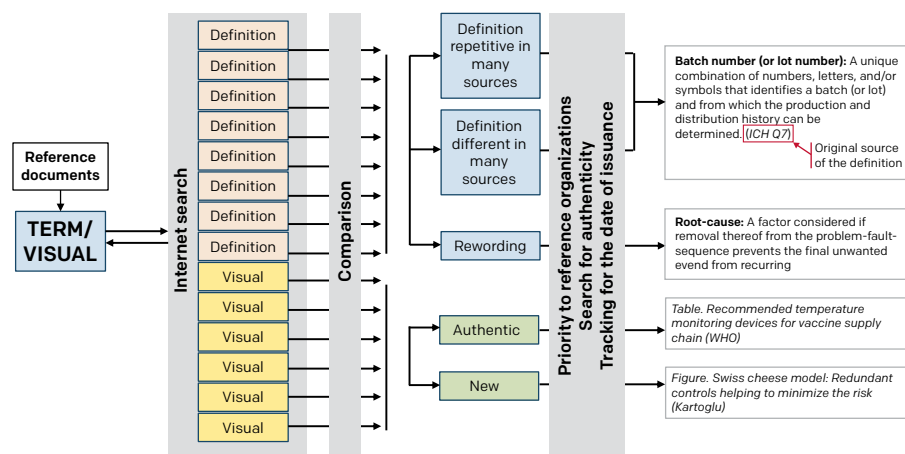
Dictionaries define “quality” as “the standard of something when compared to other things like it” or as “how good or bad”. When we speak of “pharmaceutical/vaccine product quality”, there is much more that needs to be considered aside from the development, approval and manufacturing aspects. All products spend considerable periods of time at storage facilities, in transport between warehouses, at hospitals, pharmacies, health centres and at homes of end-users. Therefore just offering a “quality” product to the market is not enough. The product’s quality must be maintained throughout its life until it is consumed.

Cold chain is an area specific to time and temperature sensitive pharmaceutical products. Violating the rules of cold chain safety gravely affects the quality of a product. When we speak of “quality”, we should not only think about the product itself, but also everything else outside its box.

The spectrum of this glossary goes from product development and clinical trials to legislation around regulatory functions; from manufacturing to storage and dispatch activities and to post-marketing surveillance. It covers a comprehensive list of systems, procedures, and tools used at all levels that one way or another touch the issue of product quality.

What you have in your hand is not a simple glossary. Under many terms, in addition to their definitions, you will find additional information and perspectives on their uses. Wherever possible, tables, flow charts, decision tables, illustrations, sketches, and photographs are included.

Many colleagues asked me what process I followed in creating this volume. Here is how I would map out the process I followed.



I started browsing the reference documents first. This helped me in expanding the pool of terms. For each term, I ran an extensive Internet search downloading all top 25 hits. These included pages from as common as Wikipedia to specific documents from reference organizations as well as books and peer-review articles. On the top of my list I put the definitions referenced by ICH, ISO, IATA, WHO, PDA and others.

The next step was to compare the definitions and find the overlapping ones, as well as deviations and in some cases gaps. Many definitions were repeated word by word in various sources without indicating the real source. In order to find out the origin, I worked on the publishing dates of the information involved. In some cases – but very seldom, based on everything I had in hand, I redefined the term. Some definitions included other terms within them. In the end I accumulated 730 terms.

I used a similar approach for the visuals. I printed out the existing visuals, and went through each and every single one to decide whether it was necessary to create a new one or to modify the existing one. In cases where the visual (be it table, flow-chart, graph, illustration or photograph) was authentic, I included it as it was. In other cases, I created the visuals myself or modified them from their original sources.

In the definitions, the *italic* references in parenthesis indicate the original source of the definition. My own or modified definitions do not have such indications. The same approach was also used for the visuals.

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I worked on this document during my summer vacation of 2015, as well as during the long nights after work and the weekends between Switzerland and France. I dedicate this work to my loving wife Nellie and my daughter Deniz Nala, who are always there for me with their love and support. I feel grateful to my colleagues from WHO, UNICEF, the industry, national country programmes and national regulatory agencies with whom I discussed some of the terminology.

Contents

Foreword James Vesper	v	Active pharmaceutical ingredient (API)	6
Foreword Thomas C. Reeves	vii	Active systems	6
Behind the pages	ix	Adjustments	6
Abbreviations	xxvii	Adjuvant	6
1-2-3		Administrative adjudication	6
3PL	1	Advance shipping notice	6
4PL	1	Advanced phase change materials (PCMs)	7
5-whys	1	Adventitious agents	7
A		Adverse drug reaction (ADR)	7
ABC analysis	3	Adverse event (AE)	7
Absorption cycle refrigerator	4	Adverse event(s) following immunization (AEFI)	7
Accelerated stability studies	4	AEFI core variables	8
Accelerated testing	4	AEFI investigation	8
Acceptable temperature range (for refrigerators)	4	Airliner	9
Acceptance criteria	5	Air waybill (AWB)	9
Accident	5	ALARA principle	10
Accuracy	5	ALARP principle	11
Active cooling	5	Allocation system	11

Alpha error	11	Beneficence	18
Analytical procedure	11	Beta error	18
Ancillary packaging components	11	Bias (statistical & operational)	18
Antibody	11	Bin card	18
Antigen	11	Bioburden	18
Antigenic drift	11	Biodistribution study	18
API starting material	11	Bioequivalence	18
Appreciation (so what) technique	12	Bioequivalence test	19
Arrhenius equation	12	Biological indicators	19
Article 5 country	13	Biological tests (bioassay)	19
Article 58 (EMA's scientific opinion)	13	BIPM	19
Attack rate	13	Blind review	19
Audit	13	Blinded/unblinded (data)	19
Audit (of clinical trial)	14	Blinding	20
Audit (of transport)	14	Booster vaccination	20
Audit certificate	14	Bracketing	20
Audit report	14	Bridging studies	20
Audit trail	14	Buffer stock	20
Authorization holder	14	Bulk purified plasmid (drug substance)	20
Authorized person	14	Bulking factor	20
Autonomy (solar refrigerators)	14		
Auxiliary equipment	14		
Average monthly consumption (AMC)	15		
		C	
		C_{max}	21
		Calibration	21
		CAPA (Corrective and preventive actions) system	21
		Care delivery problems	22
		Case-control study	22
		Case definition	23
		Case report form (CRF)	23
		Causal association	23
		Causal factor	23
		Causality assessment	23
		Cause	24
B			
Bacteria	16		
Baseline samples	16		
Batch	16		
Batch card	16		
Batch number (or lot number)	17		
Batch release	17		
Batch release certificate	17		
Battery powered solar refrigerator	18		

Cause and effect diagrams	25	Community	40
Center of Excellence for Independent Validators in Pharmaceutical Logistics (CEIV)	25	Community investigation	40
Change management	25	Commutability	40
Change management system	25	Comparator product	40
Charter	26	Complaint	40
Chemical indicators	26	Component	40
Chlorofluorocarbons (CFCs)	27	Compression cycle refrigerator	40
Class A packaging	27	Conditioning	40
Class ABC packaging	27	Conduction	41
Class B packaging	28	Confidentiality	41
Class C packaging	28	Conflict of interest	41
Client	28	Conformity	41
Climate zone (for refrigerators)	28	Conjugated vaccine	41
Climatic zone	28	Consolidation centre	42
Clinical trial/study	35	Constitution	42
Clinical trials registry	36	Consumption records	42
Cluster	36	Container closure system	42
Cluster sampling	36	Contamination	43
Coefficient of heat transfer	37	Continuous process validation	43
Cohort study	37	Contract	43
Coincidental event	37	Contract manufacturer	43
Cold	37	Contract research organization (CRO)	43
Cold chain	38	Contributing cause	43
Cold chain monitor (CCM)	38	Contributing factors	43
Cold life	38	Control	43
Cold room	38	Control (of disease)	43
Cold store	38	Control strategy	43
Combined vaccine	38	Controlled or hazardous products	44
Commitment batches	39	Controlled temperature chain (CTC)	44
Commodities	39	Controller	45
Common carrier	39	Controller, critical	45
Common technical document (CTD)	39	Controller, non-critical	45
		Convection	45
		Cool	45

Cool down time	45	Denominator	52
Cool life	45	Dependent variable	52
Cool life test	45	Design-build	52
Cool water-pack	45	Design failure	52
Coolant	46	Design qualification (DQ)	52
Cooling	46	Design space	52
Coordinating investigator	46	Detectability	52
Correction	46	Developing Countries	
Corrective action	46	Vaccine Manufacturers	
Cost benefit analysis	46	Network (DCVMN)	52
Cost effectiveness analysis	46	Deviation	53
Court decisions	46	DFSS	53
Critical control point (CCP)	47	Diagnostic odds ratio	53
Critical deviation	47	Diluent	53
Critical process parameter (CPP)	47	Direct access	53
Critical quality attribute (CQA)	47	Dissipation	54
Cross-contamination	47	Distributor	54
Cross-dock centre	47	DMADV	54
Cross-sectional study	48	DMAIC	55
Cryogenic dry/vapour shipper	48	Documentation	55
Cycle stock	48	Dosage form	55
D		Double-dummy	56
Damage indicator	49	Drill-down technique	56
Dangerous goods	49	Dropout (clinical trial)	56
Dangerous goods regulations (DGR) ..	50	Dropout rate	56
Data and safety monitoring board		Drug product	57
(DSMB)	50	Drug substance	57
Dead space (in syringes)	51	Dunnage	57
Declaration of Helsinki (DoH)	51	E	
Decrees	51	Earliest expiry first out (EEFO)	58
Deductive reasoning	51	Electronic data integrator (EDI)	58
Defects per million opportunities		Electronic data logging	
(DPMO)	51	monitor (EDLM)	59

Electronic temperature indicator (ETI)	59	Failure cause	75
Electronic temperature monitoring and event logger system	60	Failure effect	75
Elimination (of disease)	60	Failure mode	75
Emergency escape or first-aid signs	60	Failure mode and effects analysis (FMEA)	76
Endemic	61	Failure mode, effects, and criticality analysis (FMECA)	77
Environmental management system	61	False discovery rate	77
Epidemic	62	False negative rate	77
Epidemiology	62	False omission rate	77
EPP	62	Fault tree analysis (FTA)	78
EPS	62	Feedback report	80
Equivalence trial	63	Finished pharmaceutical product (FPP)	81
Eradication (of disease)	63	Firefighting signs	81
Essential documents (clinical trials)	64	First in first out (FIFO)	81
EUR pallet	71	Fishbone diagram	81
Event tree analysis (ETA)	71	Flooded battery	82
Excipient	72	Forecasting	82
Expected monetary value (EMV)	72	Freeze indicator	82
Expedited review	72	Freeze-thaw (cycle) studies	83
Experimental study	73	Freezer room	83
Expert Committee for Biological Standardization (ECBS)	73	Frozen control	83
Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)	73	Full quality assurance	83
Expiry date	74		
Exposure	74		
External distribution	74		
F		G	
Facility management	75	g-force	84
Failure	75	GAVI	84
		Generic products	84
		Global Advisory Committee on Vaccine Safety (GACVS)	85
		Global Vaccine Safety Blueprint	85
		Global Vaccine Safety Initiative (GVSI)	86

Globally Harmonized System of Classification and Labelling of Chemicals (GHS)	87
Gold standard	87
Good clinical practice (GCP)	87
Good laboratory practice (GLP)	88
Good regulatory practice (GRP)	88
Gross storage capacity	89
Grossing factor	89

H

Harm	90
Hazard	90
Hazard Analysis and Critical Control Point (HACCP)	90
Hazard and Operability Studies (HAZOP)	92
Hazard labels	94
Hazard pictograms	95
Hazard statement	95
Hazardous materials	95
Heat	95
Heat of fusion	95
Heat transfer	95
Herbal products	95
Hierarchical holographic modelling (HHM)	95
Holdover time	99
Host	99
Human error	99
Humidity (relative humidity (RH))	99
Hydrocarbons (HCs)	100
Hydrochlorofluorocarbons (HCFCs) ..	100
Hydrofluorocarbons (HFCs)	100
Hydrofluoroolefin (HFO)	100

I

Ice-lined refrigerator	101
Ice-pack	101
Ice-water bath	101
ICH	102
Immune	103
Immunity	103
Immunity (acquired)	104
Immunity (active)	104
Immunity (herd)	104
Immunization anxiety-related reaction	104
Immunization card	104
Immunization error-related reaction ..	104
Immunization register	104
Immunization safety	106
Immunogenicity	106
Impact indicator	106
Impartial witness	106
Impermeable containers	106
Impurity	106
Impurity profile	106
In use	106
Incidence	106
Incident	106
Incoterms	106
Independent Data-Monitoring Committee (IDMC)	107
Independent ethics committee (IEC) ..	107
Independent variable	109
Inductive reasoning	109
Informed consent	109
Inspection	110
Installation qualification (IQ)	110
Institutional Review Board (IRB)	110

Instrument	111	L	
Insulated shipper	111	Label	120
Insulated shipping container	111	Labelling (for APIs and FPPs)	121
Intention-to-treat principle	111	Lanes	122
Interim clinical trial/study report	111	Last mile	122
Intermediate vaccine store	111	Latent heat	122
Intermediates	111	Lattice	123
Internal distribution	111	Law	124
International Clinical Trials Registry Platform (ICTRP)	112	Lead time	124
International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)	112	Lean manufacturing	124
International Medical Products Anti-Counterfeiting Taskforce (IMPACT)	112	Lean thinking	124
International nonproprietary name (INN)	112	Legal manufacturer	124
International Pharmacopoeia (Ph. Int.)	113	Legally acceptable representative	125
International standards for clinical trial registers	113	Lifecycle	125
Inventory control card	113	Linearity	125
Inventory control system	114	Long-term stability studies	125
Inventory turnover	114	Loss report	126
Investigational product	114	Losses	126
Investigator	115	Lot	126
Investigator's brochure (IB)	115	Lot number	127
ISO container	116	Lot release	127
ISO pallets	117	Lot release certificate (LRC)	127
Issue voucher	117	Lot size stock	127
Issues data	118	M	
K		Main equipment	128
Key fob	119	Maintenance management	128
Key operating parameters	119	Management Review of Process Performance and Product Quality	128
		Mandatory signs	129
		Mapping	129
		Marketing authorization	129
		Marketing partner	129
		Masking	129

Master file	129	Negative predictive value	138
Master formula	129	Net storage capacity	138
Matrixing	130	Non-Article 5 country	138
Maximum payload	130	Non-clinical evaluation of vaccines	139
Maximum rated ambient temperature	130	Non-clinical study	139
Maximum stock level	130	Non-inferiority trial	139
Mean kinetic temperature (MKT)	130	Non-maleficence	139
Medical care of trial subjects	130	Numerator	139
Medicinal product	131	Nylon	140
Medicine	131		
Medicines regulatory authority	131	O	
Meta-analysis	131	Ongoing stability study	141
MIL-STD-105E	131	Operational qualification (OQ)	141
Min/max	134	Out-of-specification	141
Minimum payload	134	Outbreak	142
Minimum rated ambient temperature	134		
Minimum stock level	134	P	
Minor AEFI	134	Package insert	143
Mixed systems	134	Packaging	145
Model Formulary (WHO)	134	Packing slip	145
Model List of Essential Medicines	134	Packout	145
Monitor	135	Pallet	145
Months of supply	135	Pallet shipper	145
Montreal Protocol	135	Pandemic	146
Multi dose vial policy (MDVP)	136	Passive cooling	146
Multicentre trial	136	Passive systems	146
Multisource (generic) pharmaceutical product	136	Performance qualification (PQ)	146
		Performance, Quality and Safety (PQS)	146
		Perishable Cargo Regulations (PCR)	147
		Perishables	147
		Pharmaceutical equivalents	147
		Pharmaceutical product	147
		Pharmaceutical Quality System (PQS)	148
N			
National control laboratory (NCL)	137		
National regulatory authority (NRA)	137		
Negative likelihood ratio	138		

Pharmacopoeia	148	Product realization	160
Pharmacopoeial text	148	Product summary file	160
Pharmacovigilance (vaccine)	148	Production batch	160
Physical inventory	150	Prohibitory signs	160
PIC/S	152	Proportional rate	161
Pictogram	153	Protection at birth (PAB) indicator	161
Pilot-scale batch	153	Protocol	162
PIR (Polyisocyanurate)	153	Protocol amendment	162
Placebo control	153	Provisional shelf-life	162
Positive likelihood ratio	153	Public private partnership	162
Positive predictive value	154	Pull system	163
Post-marketing surveillance	154	PUR	163
Potency	154	Push system	163
Pre-clinical evaluation of vaccine	154		
Pre-clinical toxicity study	154	Q	
Pre-exposure trial	154	Qualification	165
Precautionary pictograms	154	Qualification protocol	165
Precautionary statement	155	Qualified person (QP)	165
Precipitation coefficient	156	Qualified third party	165
Precision	156	Quality	165
Preliminary Hazard Analysis (PHA)	156	Quality agreement	166
Preliminary Risk Analysis (PRA)	156	Quality assurance	166
Prequalified shipping container system	158	Quality audit	167
Prevalence	158	Quality by design (QbD)	167
Preventive action	158	Quality control (QC)	167
Primary batch	158	Quality management system (QMS)	167
Primary container	158	Quality manual	168
Primary vaccination	158	Quality risk management	169
Primary vaccine store	158	Quality system	170
Process failure	158	Quality target product profile (QTPP)	170
Process Performance and Product Quality Monitoring System	158	Quantity in hand	170
Process validation	160	Quarantine	170
Product characterization	160		

R

R-value (insulation)	171
Radiation	172
RAG status	172
Random number	172
Random sampling	172
Randomization	172
Rate	172
Rate of consumption	172
Rational use of medicines	172
Raw data	173
Reactogenicity	173
Reagent	173
Real-time, real-condition stability studies	173
Recall	173
Receiving record	174
Records	174
Refrigerant	174
Refrigerated container or reefer	174
Refrigerated vehicle	175
Refrigeration equipment	175
Regulation	175
Relabelling	175
Release specification	175
Remote temperature monitoring	176
Reorder level	176
Repackaging	176
Reproductive rate	176
Request indicator	176
Requisition and issue voucher	176
Requisition system	178
Research participant	178
Reseller	178

Residual risk	179
Re-test date	179
Re-test period	179
Risk	179
Risk analysis	179
Risk assessment	179
Risk communication	180
Risk control	180
Risk evaluation	180
Risk identification	180
Risk management	180
Risk management framework	180
Risk management process	180
Risk matrix	181
Risk ranking and filtering (RRF)	183
Risk reduction	184
Risk review	184
Risk scales (used in risk assessment)	184
Risk treatment	186
Root-cause	187
Root-cause analysis	187
Route of administration	188

S

Safety and tolerability	189
Safety stock	189
Sample size	189
Seasonal packaging solution	189
Secondary attack-rate study	189
Secondary pack or carton or market package	190
Sedimentation rate	190
Semi-permeable containers	190
Sensitivity	190

Sensor	190	Spurious/falsely-labelled/falsified/ counterfeit (SFFC) medicines	206
Serious adverse event or adverse drug reaction	190	Stability	206
Serious AEFI	192	Stability budget	206
Seroconversion	192	Stability indicating methods	207
Service delivery point	192	Stability indicating parameters	207
Service delivery problems	192	Stability studies (stability testing)	207
Service level agreement (SLA)	192	Stability tests	208
Session size	192	Staging area	208
Severity	192	Stakeholder	208
Shake test	193	Standard deviation	208
Shelf-life	197	Standard operating procedure (SOP)	208
Shelf-life specifications	197	Standby generator	208
Shipping indicators	197	Starting material	208
Shipping lane	200	Statute	208
Shipping system	200	Stock card	209
Signal (safety signal)	200	Stock keeping records	209
Significant change	200	Stock-keeping unit (SKU)	209
Six sigma	200	Stock out	209
Solar array	202	Storage conditions (of APIs)	209
Solar direct-drive refrigerator	202	Storage temperatures	210
Solar irradiance	202	Storage unit temperature/ humidity distribution	210
Solar module	202	Store ledger	211
Solvent	202	Stress testing	211
Source data	202	Stress testing (of the API)	211
Source documents	202	Stress testing (of the FPP)	212
Spare parts	202	Study product	212
Specific and proportional vaccine wastage rates	202	Study protocol	212
Specific attack rate	205	Sub-investigator	212
Specific rate	205	Subject/trial subject	212
Specification	205	Summary report	212
Specificity	206	Supercooling	213
Sponsor	206	Superiority trial	213
Sponsor-investigator	206		

Supply chain	214	Threshold indicator	224
Supporting stability data	214	Time and temperature sensitive label (IATA)	224
Surveillance	214	Time and temperature sensitive pharmaceutical product (TTSP)	225
Suspect product	214	Time-temperature integrators (TTIs)	225
Suspected immunization error	214	Traceability	225
Swiss cheese model	215	Transaction records	225
Systematic sampling	216	Transport temperature profile	225
T		Trans-shipment point	225
T _{max}	217	Treaties	226
Technical agreement	217	Trial site	226
Technical Report Series (TRS)	217	Trial subject	226
Temperature control device	218	Triple point	226
Temperature Control Regulations (TCR)	218	TT2+ coverage indicator	226
Temperature-controlled	218	Type I error	227
Temperature excursion	218	Type II error	227
Temperature-modified	218	Type-examination	228
Temperature monitoring	218	Type-testing	228
Temperature monitoring device	220	U	
Temperature stabilizing medium	220	ULD regulations	229
Temperature zone symbols for refrigerators	221	Uncertainty	229
Tertiary pack or carton	221	Uncertainty (of measurement)	229
Therapeutic equivalence	221	Undercooling	230
Thermal equilibrium	222	Uniclass	230
Thermal stability as lot release test	222	Unit load device (ULD)	230
Thermal time constant	222	Universal packaging solution	230
Thermistor	222	Uppsala Monitoring Centre (UMC)	230
Thermocouple	222	User requirement specification (URS)	231
Thermolabile	223	Utilization factor	231
Thermosensitivity	223	Utilization period	231
Thermostability	224		
Third-party accreditation	224		

V	
Vaccination coverage	232
Vaccination failure	232
Vaccine Arrival Report (VAR)	232
Vaccine carrier	233
Vaccine cold box	233
Vaccine effectiveness	234
Vaccine (protective) efficacy	234
Vaccine Presentation and Packaging Advisory Group (VPPAG)	234
Vaccine product	235
Vaccine product related reaction	235
Vaccine quality defect-related reaction	235
Vaccine storage capacity	235
Vaccine usage rate	235
Vaccine vial monitor (VVM)	235
Vaccine wastage factor	239
Vaccine wastage rate	240
Vaccine wastage rate (in storage facilities)	241
Vaccines	242
Validation	242
Validity (of a diagnostic test)	242
VEN analysis	243
Vented shipping box	244
VIP	244
Virus	244
Volume per dose	244
Vulnerable subjects	246
W	
Warm life test	247
Warm water-pack	247
Water-pack	247
Water-pack freezing capacity (kg/24 hrs)	247
Well-being (of the trial subjects)	247
Well-established medicines	248
Well-established medicines combinations	248
Well-established medicinal products	248
Work instruction	248
Working stock	248
World Medical Association (WMA)	249
X	
XPS	250
Z	
Zeroth law of thermodynamics	251

References	253
Recommended videos	263
A year in the life of a vaccine by Kevin O'Donnell	263
Cold chain challenges everywhere by Simona Zipursky	263
Controlled temperature chain (CTC): Delivering vaccines more easily (episode 1 of 3) by World Health Organization	264

Controlled temperature chain (CTC): Implementing in the field (episode 2 of 3) by <i>World Health Organization</i>	264
Controlled temperature chain (CTC): Future development (episode 3 of 3) by <i>World Health Organization</i>	264
Documents, records and record management by <i>James Vesper</i>	265
Exploitation of stability data to reach the unreached by <i>Umit Kartoglu</i>	265
Five senses: Vaccine Vial Monitors by <i>World Health Organization</i>	266
Global Perspectives in Regulatory Oversight by <i>Rafik Bishara</i>	266
How best to use stability data for handling of time and temperature sensitive products by <i>Claude Ammann</i>	266
How does a VVM work? by <i>Denis Maire</i>	267
Interpretation of VVM in relation to other temperature monitoring devices by <i>Umit Kartoglu</i>	267
Introduction to Quality Risk Management by <i>James Vesper</i>	267
Last Mile by <i>Umit Kartoglu</i>	268
Nothing stands still by <i>World Health Organization</i>	268
Packaging design by <i>Kevin O'Donnell</i>	268
Risk assessment methods by <i>James Vesper</i>	269
Shake and Tell (video article) by <i>World Health Organization</i>	269
Step-by-step how to conduct the shake test by <i>World Health Organization</i>	269
Storage Facility Design: Cold Storage by <i>Andrew Garnett</i>	270
Storage Facility Design: Site and Buildings by <i>Andrew Garnett</i>	270
Thermodynamics by <i>Kevin O'Donnell</i>	270
Using VVM as a stock management tool by <i>Umit Kartoglu</i>	271
Vaccines beyond the cold chain by <i>Simona Zipursky</i>	271
VVMs getting smarter by <i>Umit Kartoglu</i>	271
VVM use at the most periphery by <i>Serge Ganivet</i>	272
GIFs	273
Consolidation centre	273
Cross-dock centre	273
Trans-shipment point	274
Swiss cheese model	274
ABOUT THE AUTHOR	275

Abbreviations

°C	degree Celcius
°F	degree Fahrenheit
3PL	third-party logistics (provider)
4PL	fourth-party logistics (provider)
ADR	adverse drug reaction
AE	adverse event
AEFI	adverse event(s) following immunization
ALARA	as low as reasonably achievable
ALARP	as low as reasonably practical
AMC	average monthly consumption
ANSI	American National Standards Institute
API	active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
ASTM	American Society for Testing and Materials
ATP	Agreement on the International Carriage of Perishable Foodstuffs and on the Special Equipment to be used for such Carriage
AWB	airway bill
BCG	bacilli Calmette- Guérin (tuberculosis vaccine)
BIPM	Bureau International des Poids et Mesures
BSI	British Standards Institution
CAPA	corrective and preventive action
CCM	(vaccine) cold chain monitor
CCP	critical control point
CEIV	Center of Excellence for Independent Validators in Pharmaceutical Logistics (IATA)

CFC	chlorofluorocarbon
CIOMS	Council for International Organizations of Medical Sciences
CFR	cost and freight
CIF	cost, insurance and freight
cm³	cubic centimetres
CPP	critical process parameter
CPT	carriage paid to
CQA	critical quality attribute
CRF	case report form
CRO	contract research organization
CTC	controlled temperature chain
CTD	common technical document
DCVMN	Developing Countries Vaccine Manufacturers Network
DFSS	design for six-sigma
DMADV	define, measure, analyze, design, and verify
DMAIC	define, measure, analyze, improve, and control
DoH	Declaration of Helsinki
DPMO	defects per million opportunities
DPWN	Deutsche Post World Net
DQ	design qualification
DSMB	Data and Safety Monitoring Board
DT	diphtheria-tetanus (vaccine)
DTP	diphtheria-tetanus-pertussis (vaccine)
DTwP	diphtheria-tetanus-whole cell pertussis (vaccine)
EC	ethics committee
ECBS	Expert Committee for Biological Standardization (WHO)
EDLM	electronic data logging monitor
EEFO	earliest expiry first out
EFTA	European Free Trade Association
EMA	European Medicines Agency
EML	essential medicines list
EMV	expected monetary value
EN	European standard
EPAL	European Pallet Association
EPELA	Extentio et Progressio – Authentic e-Learning
EPI	Expanded Programme on Immunization
EPP	expanded polypropylene
EPS	expanded polystyrene
ETA	event tree analysis
ETI	electronic temperature indicator
EU	European Union
EXW	Ex works

FAS	free along ship
FCA	free carrier
FEFO	first expiry first out
FIFO	first in first out
FMEA	failure mode and effects analysis
FMECA	failure mode, effects, and criticality analysis
FOB	free on board
FPP	finished pharmaceutical product
FTA	fault tree analysis
GACVS	Global Advisory Committee on Vaccine Safety (WHO)
GAPPD	The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea
GAVI	GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization)
GCC	Gulf Cooperation Council
GCP	good clinical practices
GLP	good laboratory practices
GMP	good manufacturing practices
gPPP	generic preferred product profile
GRP	good regulatory practice
GTDP	good trade and distribution practices
GUM	Guide to the Expression of Uncertainty in Measurement
GVSI	Global Vaccine Safety Initiative (WHO)
GWP	global warming potential
HACCP	hazard analysis and critical control point
HAZMAT	hazardous materials and items
HAZOP	hazard and operability studies
HC	hydrocarbons
HCFC	hydrochlorofluorocarbon
HFC	hydrofluorocarbon
HFO	hydrofluoroolefin
HDPE	high density polyethylene
HepB	hepatitis B (vaccine)
HHM	hierarchical holographic modelling
Hib	<i>Haemophilus influenza</i> type b (vaccine)
hPa	hectopascal
HPV	human papillomavirus vaccine
hr	hour
IATA	International Air Transport Association
IB	investigator's brochure
ICAO	International Civil Aviation Organization
ICDRA	International Conference of Drug Regulatory Authorities

ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICTRP	International Clinical Trials Registry Platform
IDMC	Independent Data-Monitoring
IEC	independent ethics committee
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMO	International Maritime Organization
IMPACT	International Medical Products Anti-Counterfeiting Taskforce (WHO)
INN	international nonproprietary name
IPAC	Immunization Practices Advisory Committee (WHO)
IPV	inactivated polio vaccine
IQ	installation qualification
IRB	institutional review board
ISO	International Organization for Standardization
ISPE	International Society for Pharmaceutical Engineering
ISTA	International Safe Transit Association
JCGM	Joint Committee for Guides in Metrology
JE	Japanese encephalitis (vaccine)
kg	kilogram
LCD	liquid crystal display
LDPE	low density polyethylene
LMIC	low and middle income countries
LRC	lot release certificate
LVPs	large volume parenterals
m	meter
mA	miliampere
MDVP	multi dose vial policy
MIL-STD	military standard
MKT	mean kinetic temperature
MMR	mumps-measles-rubella (vaccine)
MNT	maternal and neonatal tetanus
MR	measles-rubella (vaccine)
n/a	not applicable
NCL	national control laboratory
NGO	non-governmental organization
NRA	national regulatory authority
NTC	negative temperature co-efficient
ODS	ozone-depleting substances
OPV	oral polio vaccine

OTIF	Intergovernmental Organization for International Carriage by Rail (abbreviation is derived from the original French name "L'Organisation intergouvernementale pour les transports internationaux ferroviaires")
OQ	operational qualification
PAB	protection at birth
PAHO	Pan American Health Organization
PCM	phase change material
PCR	Perishable Cargo Regulations (IATA)
PDA	Parenteral Drug Association
PDF	portable document format
pH	potential of Hydrogen
Ph. Int.	International Pharmacopoeia (WHO)
PHA	preliminary hazard analysis
PIC/S	The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PIR	polyisocyanurate
PQ	performance qualification
PQS	Performance, Quality and Safety (project of WHO)
PQS	pharmaceutical quality system
PRA	preliminary risk analysis
PUR	polyurethane
QA	quality assurance
QbD	quality by design
QP	qualified person
QTPP	quality target product profile
RAG	red, amber, green
REB	research ethics board
RH	relative humidity
RRF	risk ranking and filtering
SFFC	spurious/falsely-labelled/falsified/counterfeit (medicines)
SKU	stock-keeping unit
SLA	service level agreement
SMS	short message service
SOP	standard operating procedure
TCR	Temperature Cargo Regulations (IATA)
Td	tetanus toxoid and diphtheria (reduced component) vaccine
TGA	Therapeutic Goods Administration (Australia)
TRS	Technical Report Series (WHO)
TT	tetanus toxoid (vaccine)
TTI	time-temperature integrator
TTSP	time and temperature sensitive pharmaceutical product
ULD	unit load device

ULDR	ULD regulations
UMC	Uppsala Monitoring Centre
UNEP	United Nations Environment Programme
UNICEF	United Nations Children Fund
URS	user requirement specification
USB	universal serial bus
USFDA	United States Food and Drug Administration
USP	United States Pharmacopeia
VAR	vaccine arrival report
VEN	vital, essential, nonessential
VIP	vacuum insulation panels
VPPAG	Vaccine Presentation and Packaging Advisory Group
VVM	vaccine vial monitor
WHO	World Health Organization
WMA	World Medical Association
XPS	extruded polystyrene

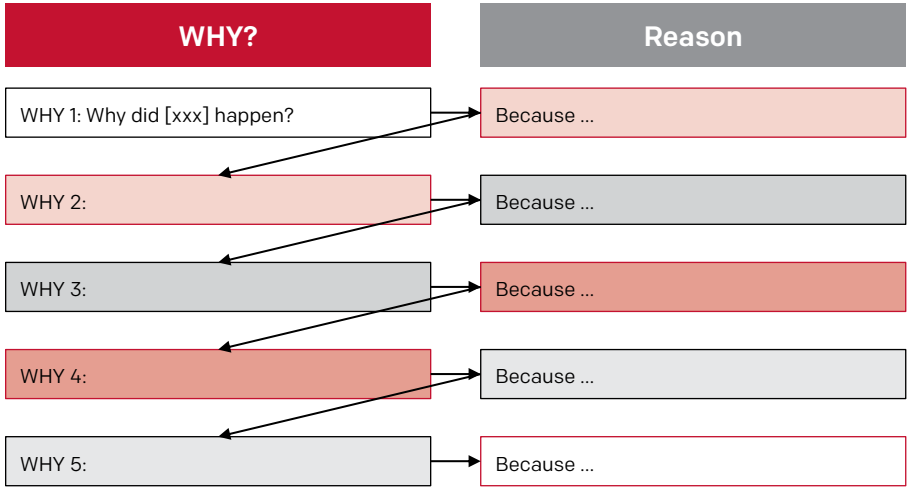
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3PL: Third-party logistics provider – a firm that provides service to its customers of outsourced (or “third party”) logistics services for part, or all of their supply chain management functions. (*WHO*)

4PL: Fourth-party logistics provider - a general contractor who manages other 3PLs, truckers, forwarders, custom house agents, and others, essentially taking responsibility for a complete logistics process for the customer. (*WHO*)

5-whys: An iterative question asking technique used in the “analyze” phase of the Six Sigma DMAIC (define, measure, analyze, improve, control) methodology to explore the cause-and-effect relationships underlying a particular problem. It does not involve any data segmentation, hypothesis testing, regression or other advanced statistical tools, and in many cases can be completed without a data collection plan. The 5 whys typically refers to the practice of asking, five times, why the failure has occurred in order to get to the root cause/causes of the problem. The outcome depends upon the knowledge and persistence of the people involved. In a typical 5 whys exercise, each answer typically forms the next question. For example, when you ask why there was a temperature excursion and answer as because frozen ice-packs were used, the second question automatically forms itself as “why frozen ice-packs were used?” Also see *fishbone diagram*.

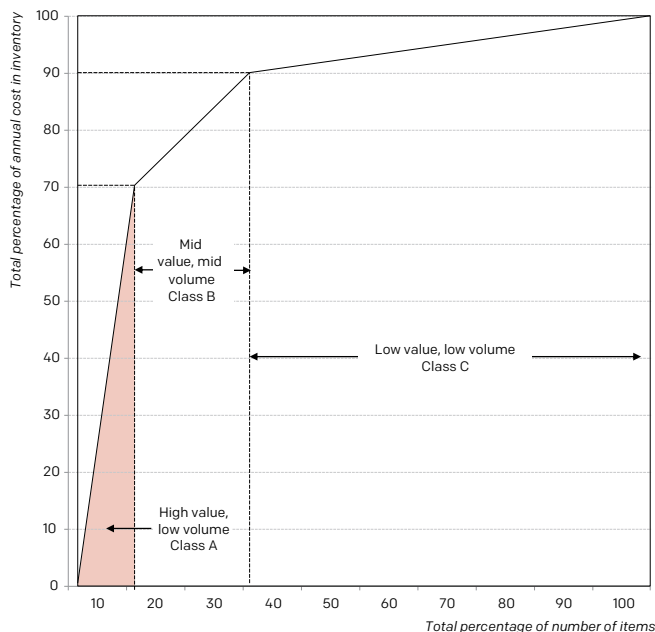
5-whys: Answers establishing the next “why” question (Kartoglu)



A

ABC analysis: Tool for reviewing stock movement, which categorizes items by the volume and value of consumption during a specific period of time, usually one year. Class A items – 10-20% of items, representing 75-80% of expenditures - are mostly high-volume, fast-moving medicines. Class B items are usually 10-20% of items, and

ABC analysis (Kartoglu)



15–20% of expenditures. Class C items often represent 60–80% of the items but only about 5–10% of the total expenditures; these are the low-volume, slow-moving items. Thus, class C is a good place to look for items that might not be needed in stock at all times (*WHO*). See also *VEN analysis*.

Absorption cycle refrigerator: Refrigerator that uses a heat source such as gas or kerosene to drive the cooling system. A less efficient alternative to compression cycle refrigerators, absorption cycle refrigerators are most frequently used in areas with unreliable grid electricity. Currently there are no PQS prequalified absorption cycle refrigerators. (*WHO*)

Accelerated stability studies: Studies designed to determine the rate of change of vaccine properties over time as a consequence of the exposure to temperatures higher than those recommended for storage. These studies may provide useful support data for establishing the shelf-life or release specifications but should not be used to forecast real-time, real-condition stability of a vaccine. They could also provide preliminary information on the vaccine stability at early developmental stages and assist in assessing the stability profile of a vaccine after manufacturing changes. (*WHO*)

Accelerated testing: Studies designed to increase the rate of chemical degradation and physical change of an API or FPP by using exaggerated storage conditions as part of the stability testing programme. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes. (*WHO*)

Acceptable temperature range (for refrigerators): The acceptable temperature range for storing vaccine is +2°C to +8°C. However, WHO PQS prequalification programme indicates that transient excursions outside this range will be tolerated, within the following limits:

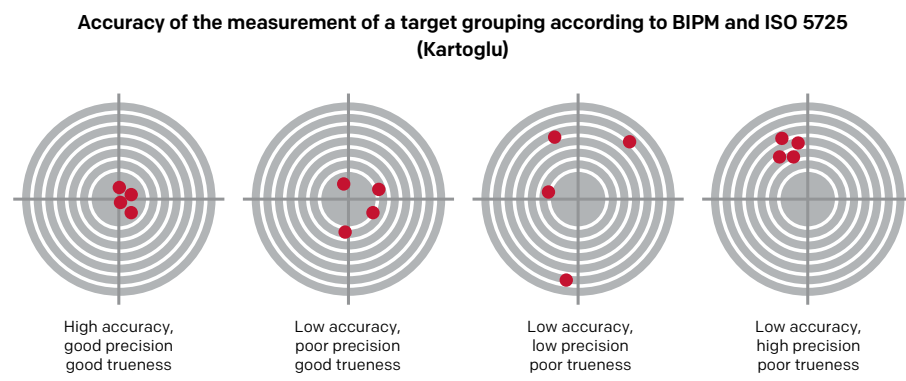
- No excursion must exceed +20°C.
- No excursion must reach 0°C.

The cumulative effect of any excursions within the above range is assessed over the five day period of the day/night test. For this test, the calculated mean kinetic temperature (MKT) must remain within the range +2°C to +8°C when the default activation energy is set at 83,144 kJ per mol. using the recorded temperature data, an MKT figure is calculated for each sensor. The worst-case result determines the outcome of the test. Excursions in other tests are noted and must not exceed the defined upper and lower limits. (*WHO*)

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of test results. (*ICH Q6A*)

Accident: An adverse outcome that was not caused by chance or fate. Most accidents and their contributing factors are predictable and the probability of their occurrence may be reduced through system improvements. (*Canadian Patient Safety Dictionary*)

Accuracy: The closeness of a measurement to the true value. When the term is applied to sets of measurements of the same measurand, it involves a component of random error and a component of systematic error. In this case trueness is the closeness of the mean of a set of measurement results to the actual (true) value and precision is the closeness of agreement among a set of results. (*ISO 5725-1*)



The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness. (*ICH Q2/R1*)

Accuracy is also used as a statistical measurement of how well a binary classification test correctly identifies or excludes a condition. In statistics it is also called as "rand accuracy" or "rand index".

$$\text{Accuracy} = \frac{\text{Number of true positives} + \text{number of true negatives}}{\text{Total number of cases examined}}$$

Active cooling: See *active systems*.

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. (WHO)



Active air cargo container (Envirotainer)

Active systems: Externally powered or on-board powered systems using electricity or another fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g., cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air containers). (WHO)

Adjustments: Administrative corrections - e.g., a physical stock count that is different from quantity on stock keeping records. Also used for all losses within the facility (breakage, expiry, freezing, missing inventory, theft). (WHO)

Adjuvant: Substance that is intended to enhance relevant immune response and subsequent clinical efficacy of the vaccine, but does not in itself confers immunity. Adjuvants help activate the immune system, allowing the antigens - pathogen components that elicit an immune response - in vaccines to stimulate a response that leads to long-term protection. Most common adjuvants used in vaccines are aluminum hydroxide and aluminum phosphate. (WHO)

Administrative adjudication: A trial-like process in which the agency applies existing legal rules to particular situations. In addition to adopting regulations, administrative agencies also make law through the process of adjudication. Licensing decisions are a particular form of administrative adjudication, in which an agency grants authority to an individual or organization to engage in a particular activity. The drug approval process is an example of a licensing decision. In most countries, drugs may not be marketed or distributed until they have been approved by regulatory authorities for at least one indication. (WHO)

Advance shipping notice: A notification of pending deliveries, similar to a packing list, usually sent in an electronic format. It provides information to the destination's receiving operations well in advance of delivery, and tends to impact logistics in reducing receiving cost, confirming accuracy and bringing flexibility. (WHO)

Advanced phase change materials (PCMs): Temperature stabilizing media (sometimes referred to as refrigerants), chemically engineered so that their latent heat of fusion occurs at a temperature other than 0°C, phasing from one state of matter to another (e.g., liquid to solid) at a pre-formulated temperature. Such materials typically comprise oils, salts, or paraffin. (*WHO*)



**A VIP container with
23°C PCM as refrigerant
(Gönendik)**

Adventitious agents: An infectious agent that is introduced into a therapeutic good during collection of raw materials or the manufacturing process. Adventitious agents include mycoplasma (a type of bacteria), viruses and agents that cause transmissible spongiform encephalopathies (prions). (*TGA*)

Adverse drug reaction (ADR): In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

The old term “side effect” has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction. (*ICH E2A*)

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (*ICH E2A*)

Adverse event(s) following immunization (AEFI): Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavour-

able or unintended sign, abnormal laboratory finding, symptom or disease. If not rapidly and effectively dealt with, can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence. (WHO)

Also see *AEFI investigation* and *causality assessment*.

AEFI core variables: A set of critical variables recommended to properly managing AEFI information. This includes a unique identification of the report, the primary source of information, patient characteristics, details of the event(s) and vaccine(s) of interest and the possibility of collecting additional information if needed. (WHO)

AEFI core variables (WHO)		
IDENTITY <ul style="list-style-type: none"> ■ Date AEFI report first received at national centre ■ Country where this AEFI reported ■ Location (address) ■ Worldwide unique number 	CASE <ul style="list-style-type: none"> ■ Patient identifier ■ Date of birth (or) ■ Age at time of onset (or) ■ Age group at onset ■ Sex ■ Medical history 	VACCINE <ul style="list-style-type: none"> ■ Primary suspect vaccine name (generic) ■ Other vaccines given just prior to AEFI ■ Batch number ■ Vaccine dose number for this particular vaccine
EVENT <ul style="list-style-type: none"> ■ Date and time of vaccination ■ Date and time of AEFI onset ■ Adverse event ■ Outcome of adverse event 	REPORTER <ul style="list-style-type: none"> ■ Name of first reporter on AEFI ■ Institution / location ■ Position / department ■ e-mail ID ■ Telephone 	OTHERS <ul style="list-style-type: none"> ■ Comments (if any)

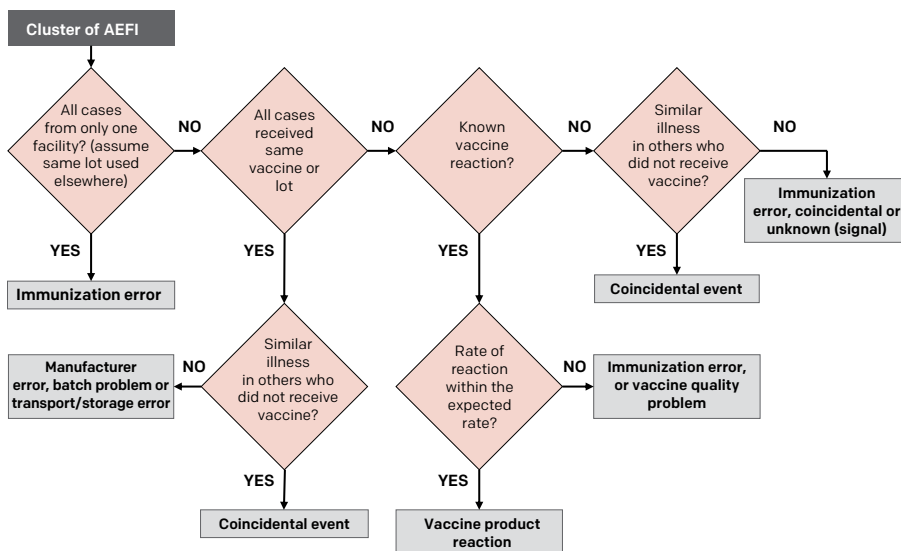
AEFI investigation: A systematic, standardized process to investigate reported serious adverse events following immunization to ascertain the underlying cause of the AEFI by:

- confirming a diagnosis and timing
- identifying details of vaccine(s) administered
- documenting the outcome of the reported adverse event
- determining whether the reported event is solitary or part of a cluster
- reviewing the operational aspects of the programme

A detailed AEFI investigation to assess causality is necessary if:

- it is serious,
- it is part of a cluster,
- it is part of a suspected signal,
- it is a suspected immunization error,
- it appears on the list of events defined for AEFI investigation, or
- it causes significant parental or public concern.

Investigating AEFI clusters – suggested steps for identifying the most likely cause of a cluster of AEFI (modified from WHO)



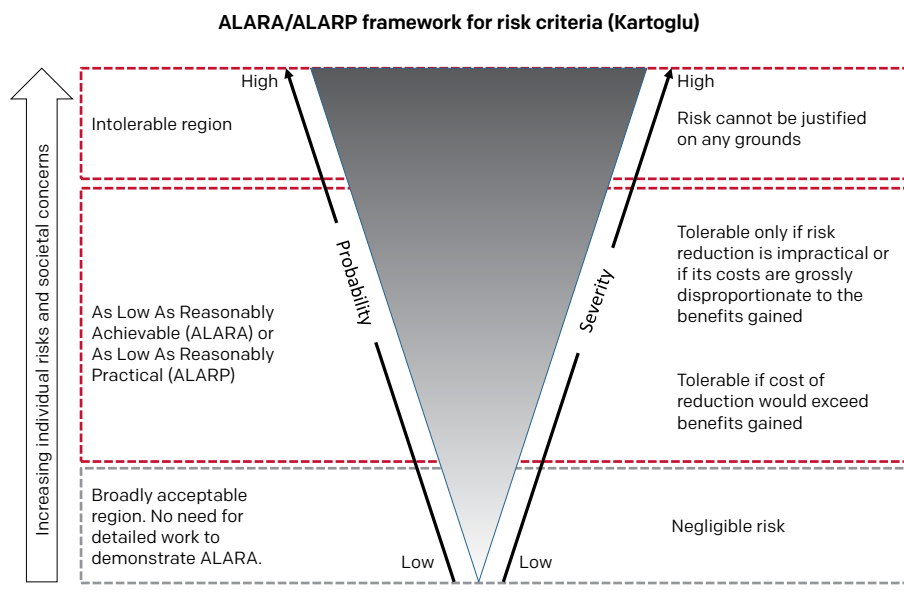
Airliner: An inflatable insulating liner that converts a corrugated shipper into a cooler. It is manufactured from high-density polyethylene and low-density polyethylene inner and outer poly films with interior baffle films made from metalized poly film. An inflated airliner has a very low conductive rate and inhibits heat flow with this internal radiant barrier technology. Its mass consists mainly of the air used for inflation. Because it is shipped uninflated (flat), airliner occupies only 4% of the warehouse space required by traditional foam boxes, resulting in low shipping and storage costs.



Airliner long range vaccine carrier – WHO PQS code E04/01 (Cold&Co)

Air waybill (AWB): A document made out by or on behalf of the shipper which evidences the contract between the shipper and the carrier(s) for carriage of goods over routes of the carrier(s). The AWB can be in the form of an airline air waybill with pre-printed issuing carrier identification, or neutral air waybill without pre-printed identification of the issuing carrier in any form. The industry is now transitioning from the use of the paper AWB to the electronic AWB. (IATA)

ALARA principle: ALARA stands for “As Low As Reasonably Achievable” and is a radiation safety principle for minimizing radiation doses and releases of radioactive materials by employing all reasonable methods. ALARA is not only a sound safety principle, but is a regulatory requirement for all radiation safety programmes. ALARA is also often applied in the pharmaceutical sector in the context of risk characterisation. In many cases ALARP (As Low As Reasonably Practical) principle is used over ALARA. The ALARP principle is that the residual risk shall be as low as reasonably practicable. To apply the principle it must be possible to show that the cost or practicality would be grossly disproportionate to the benefit gained. The principle arises from the fact that infinite resources (time, money, effort) could be used to reduce a risk but that is not achievable in the real world. It is not a simple quantitative measure of benefit against detriment. It is interlinked to the assessment if a risk is tolerable and/or controllable.



It is easier to identify unacceptable and acceptable risks. In identifying risks that fall in the ALARA/ALARP zone, the following factors should be taken into consideration as for the control measure defined:

- Effectiveness (Will it eliminate the risk or reduce the impact?)
- Benefits (What are the benefits of the controls?)
- Cost (How much will it cost?)
- Risks (Will the added control create new hazards?)
- Residual risks (What are the risks that remain after the controls being applied?)

ALARP principle: ALARP stands for “As Low As Reasonably Practical”. See ALARA.

Allocation system: See *push system*.

Alpha error: See *type I error* and *validity*.

Analytical procedure: The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, and use of the formulae for the calculation. (*ICH Q2/R1*)

Ancillary packaging components: Packaging elements used to protect the TTSP and support or enhance performance of the completed package. This may include retainers, dunnage, secondary protective packaging, and temperature data logging devices. (*WHO*)

Antibody: A protein substance produced by the immune system in response to a specific antigen that will identify and neutralize foreign material like bacteria and viruses, thus forming the basis of immunity. Each antibody recognizes a specific antigen unique to its target. Each antibody consists of four polypeptides - two heavy chains and two light chains joined to form a “Y” shaped molecule.

Antigen: Fragments or safe forms of pathogens that are used in vaccines, substances capable of stimulating an immunological response, such as the formation of antibodies. They may be proteins, polysaccharides, or complex lipids e.g., bacterial walls, the surface of erythrocytes, the protein capsule of viruses, the exotoxins and endotoxins of bacteria. The word “immunogens” reflects the fact that vaccines cause immune responses, not disease. Antigens responsible for initiating allergic reactions are called allergens.

Antigenic drift: A mechanism for variation by viruses that involves the accumulation of mutations within the antibody-binding sites so that the resulting viruses cannot be inhibited well by antibodies against previous strains making it easier for them to spread throughout a partially immune population. Antigenic drift occurs in both influenza A and influenza B viruses. (*WHO*)

API starting material: A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure. (*ICH Q7*)

Appreciation (so what) technique: An iterative question asking technique used to uncover factors that we might have ordinarily missed, also used to brainstorm solutions to problems as well as in root-cause analysis. Repetitive “so what?” question is asked to understand the implications of a fact until you draw all possible conclusions from it. Appreciation is similar to the 5 whys technique. The major difference is that it is often used to get the most information out of a simple fact or statement, while the 5 whys is specifically designed to reach down to the root of a problem.

Arrhenius equation: A formula for the temperature dependence of reaction rates. Chemical reactions are typically expected to proceed faster at higher temperatures and slower at lower temperatures. Quantitatively this relationship between the rate a reaction proceeds and its temperature is determined by the Arrhenius equation. At higher temperatures, the probability that two molecules will collide is higher. This higher collision rate results in a higher kinetic energy, which has an effect on the activation energy of the reaction. The activation energy is the amount of energy required to ensure that a reaction happens.

The effect of temperature on reaction rates using the Arrhenius equation can be calculated as follows:

$$K = A_0 e^{(-E_a/RT)}$$

In this equation, A_0 and E_a are experimentally determined constants specific to the reaction, and R is the universal gas constant (with a value of value of $8.314 \times 10^{-3} \text{ kJ mol}^{-1}\text{K}^{-1}$). The activation energy, E_a , determines how the rate changes with temperature, T , which is expressed in degrees Kelvin.

For example, for a VVM30, the optical density changes essentially linearly with

time and reaches its end-point by 30 days at 37°C , so the rate constant equals $1/30$ per day at this temperature. The end-point is the stage where the difference between the optical density of the reference ring and the optical density of the active surface (center square) of the VVM reaches zero. The experimentally determined activation energy of 27.1 kcal/mol is used to determine the optical density change for any other time–temperature combination or to plot an Arrhenius chart of the end-point as a function of temperature.



Commemorative 100th year stamps issued for Swedish chemist Svante Arrhenius (1959)

Article 5 country: The main objective of the Multilateral Fund for the Implementation of the Montreal Protocol is to assist developing country parties to the Montreal Protocol whose annual per capita consumption and production of ozone-depleting substances (ODS) is less than 0.3 kg to comply with the control measures of the Protocol. Currently, 147 of the 196 parties to the Montreal Protocol meet these criteria (they are referred to as Article 5 countries). (WHO)

Article 58 (EMA's scientific opinion): A new European pharmaceutical legislation (Regulation 726/2004) excluded licensure of vaccines and other medicinal products for exclusive use outside the European Community. The new legislation generated considerable concern since licensure of priority vaccines for developing countries would become the responsibility of the NRAs of user countries, which, in the past, relied on the regulatory evaluation of the NRA of the country of origin to assure quality. (WHO)

To ensure that there was no disruption in the supply of vaccines and medicinal products that are important for developing countries and that there is no disincentive for the timely discovery and development of these products, a consultation and collaboration between EMA and WHO led to the Article 58 in the new Regulation.

Article 58 establishes a mechanism whereby the EMA may give a Scientific Opinion, in the context of cooperation with WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. The procedure for implementation of Article 58 Scientific Opinion procedure, effective since May of 2005 begins with the request from the company to EMA to assess the eligibility of the product for Scientific Opinion. WHO's input takes place in two instances:

- evaluation of eligibility of the vaccine for Scientific Opinion by EMA;
- participation of experts proposed by WHO in the product evaluation process.

Attack rate: The biostatistical measure of frequency of morbidity, proportion of the population at risk exposed to an infectious agent who become (clinically) ill, used to project the number of victims to expect during an epidemic.

$$\text{Attack rate} = \frac{\text{Number of new cases in the population at risk}}{\text{Population at risk}}$$

Audit: A systematic evidence gathering process. Audits must be independent and evidence must be evaluated objectively to determine how well audit criteria are being met. There are three types of audits:

- first-party (self-audits or internal audits)
- second-party (external audits carried out by customers)
- third-party (external audits carried by certification bodies)

In addition to this classification, ISO also distinguishes between combined and joint audits. When two or more management systems of different disciplines are audited together at the same time, it's called a combined audit; whilst two or more auditing organizations cooperate to audit a single organization it's called a joint audit.

Audit (of clinical trial): A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s). (*ICH E6/R1*)

Audit (of transport): A systematic and independent examination of transport related activities and documents (e.g., freight bill) to verify its accuracy.

Audit certificate: A declaration of confirmation by the auditor that an audit has taken place. (*ICH E6/R1*)

Audit report: A written evaluation by the [sponsor's] auditor of the results of the audit. (*ICH E6/R1*)

Audit trail: Documentation that allows reconstruction of the course of events. (*ICH E6/R1*)

Authorization holder: The person or company in whose name the marketing authorization has been granted. This party is responsible for all aspects of the product, including quality and compliance with the conditions of marketing authorization. The authorization holder must be subject to legislation in the country that issued the marketing authorization, which normally means being physically located in the country. (*WHO*)

Authorized person: See *qualified person*.

Autonomy (solar refrigerators): Maximum number of days during which the refrigerator can continue to maintain a full vaccine load at a temperature between +2°C and +8°C when the photovoltaic panels are not generating electricity. The autonomy of a solar refrigerator measures the ability of the equipment to store vaccine during periods of heavy cloud. (*WHO*)

Auxiliary equipment: Equipment mostly used in conjunction with the equipment to be qualified but not included in the qualification package. (*WHO*)

Average monthly consumption (AMC): Average consumption data of a product over a month. (WHO)

$$\text{AMC} = \frac{\text{Start balance} + \text{Amounts received} - \text{End balance}}{\text{Number of months}}$$

AMC can be derived either from inventory records or consumption data. “Issue data” substitutes consumption data in storage facilities. However, this should be used with some caution. In an allocation/push system “issue data” might be less accurate because dispatches are not based on actual consumption.

B

Bacteria: Single-celled microorganisms which can exist either as independent (free-living) organisms or as parasites (dependent upon another organism for life).

Baseline samples: Samples that are retained under optimal storage conditions to retain biological or immunological activity and that are used for comparison purposes. The baseline samples will need to be stored at a lower temperature than that used for the reference standard. (*WHO*)

Batch: A defined quantity of starting material, packaging material or finished pharmaceutical product (FPP) processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval. (*ICH Q7*)

Batch card: A stock keeping record that keeps information about a single lot of a product. Also known as “bin card”.

A sample batch card (WHO)

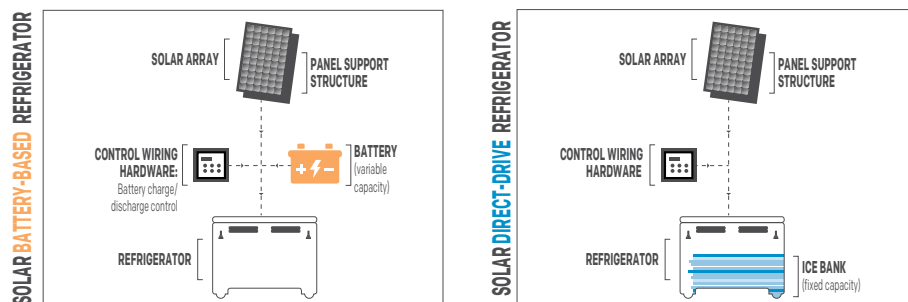
Manufacturer:		Batch number:		Expiry date:	
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[illegible]

Batch release: See *lot release*.

Pharmaceutical and vaccine quality ILLUSTRATED 17

Schematic showing difference between battery-powered and solar direct-drive refrigerators (WHO)



Battery powered solar refrigerator: Refrigerators that use solar energy stored in a battery to drive the cooling system, even during periods when solar irradiance is unavailable or limited (i.e., at night or on cloudy days). (WHO)

Beneficence: Maximizing benefits and minimizing harms and wrongs. (WHO)

Beta error: See *type II error* and *validity*.

Bias (statistical & operational): The systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value. Bias introduced through deviations in conduct is referred to as “operational” bias. The other sources of bias listed above are referred to as “statistical”. (ICH E9)

Bin card: See *batch card*.

Bioburden: The level and type (e.g., objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected. (ICH Q7)

Biodistribution study: A preclinical animal study designed to determine the distribution of a vector to sites other than the intended therapeutic site. (WHO)

Bioequivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of peak (C_{max} and T_{max}) and total exposure (area under the curve) after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same. (WHO)

Bioequivalence test: A test that determines the equivalence between the multisource product and the comparator product using in vivo and/or in vitro approaches. (*WHO*)

Biological indicators: The use of organisms to test the efficacy of sterilization processes.

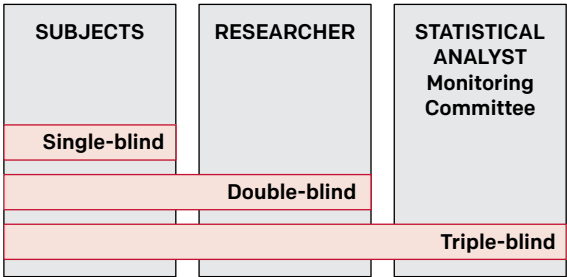
Biological tests (bioassay): A procedure for the estimation of the nature or potency of a material by means of the reaction that follows its application to some elements of a living system (examples include animals, tissues, cells, receptors and enzymes). The potency of the material being measured is often defined in IUs or, in some circumstances, may be defined in SI units, by comparison with the reaction of the system to that of a biological reference preparation. (*WHO*)

BIPM: Bureau International des Poids et Mesures (International Bureau of Weights and Measures). Created in 1875, an international standards organization, one of three such organizations established to maintain the International System of Units under the terms of the Metre Convention (Convention du Mètre). For details see <http://www.bipm.org/>

Blind review: The checking and assessment of data during the period of time between trial completion (the last observation on the last subject) and the breaking of the blind, for the purpose of finalizing the planned analysis. (*ICH E9*)

Blinded/unblinded (data): Data (or their format/presentation) are considered “blinded” when those with access to the data are not informed of the significant characteristics associated with them. Often this refers to identification of the intervention associated with the data. Data (or their format/presentation) are considered “unblinded” when those with access to them are informed of the significant characteristics (e.g., intervention) to which the data are associated. Single, double or triple “blinding” is used in experiments to minimize or eliminate the bias.

Blinding in experiments (Kartoglu)



Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware of the treatment assigned to them, and double-blinding usually refers to the subject(s), investigator(s) and, in some cases, data analyst(s) being unaware of the treatment assignment. (*ICH E6/R1*)

Booster vaccination: Vaccination given at a certain time interval after primary vaccination to enhance immune responses and induce long-term protection. (*WHO*)

Bracketing: The design of stability schedule such that only samples at the extremes of certain design factors, e.g., strength and package size, are tested at all-time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system. (*WHO*)

Bridging studies: Studies intended to support the extrapolation of efficacy, safety and immunogenicity data from one formulation, population or dose regimen to another. (*WHO*)

Buffer stock: See *safety stock*.

Bulk purified plasmid (drug substance): The purified plasmid before final formulation. It is obtained from one or more bulk harvests, and is kept in one or more containers designated as a single homogeneous production lot and used in the preparation of the final dosage form (drug product). (*WHO*)

Bulking factor: The coefficient used for calculation of volume requirements in insulated packaging, the volume of the package divided by the volume of the product it contains. In vaccine shipments, insulated packaging occupies up to 8.5 times the volume of the vaccine that it contains. WHO issues bulking factors for insulated packaging based on its prequalified vaccines list. For further details see *Guidelines on the international packaging and shipping of vaccines* (WHO/IVB/05.23) http://apps.who.int/iris/bitstream/10665/69368/1/WHO_IVB_05.23_eng.pdf

C

C_{max}: A term used in pharmacokinetics refers to the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered and prior to the administration of a second dose.

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. (*ICH Q7*)

CAPA (Corrective and preventive actions) system: A system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring (*ICH Q10*). A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9 Quality Risk Management. CAPA methodology should result in product and process improvements and enhanced product and process understanding.

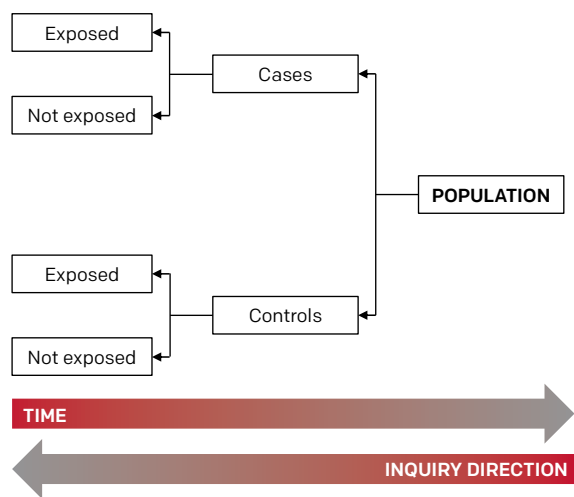
Application of corrective action and preventive action system throughout the product lifecycle (ICH Q10)

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feedforward and continual improvement.	CAPA should be used and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products which might be impacted.

Care delivery problems: Problems that are due to the direct provision of care. They arise in the process of care, usually actions or omissions by members of staff. Care delivery problems have two essential features: care deviated beyond safe limits of practice; and the deviation had at least a potential direct or indirect eventual adverse outcome for the patient, member of staff or general public. These problems are also called “active failures”. (CA Vincent)

Case-control study: An observational study in which the exposure to a particular risk factor is determined retrospectively, and the effect of this exposure is compared between individuals (the cases) who experience an event and individuals who do not (the controls).

Design of a case-control study (Kartoglu)



Case definition: A set of diagnostic criteria that must be fulfilled to confirm a case of a particular disease. Case definitions can be based on clinical criteria, laboratory criteria or combinations of the two. (WHO)

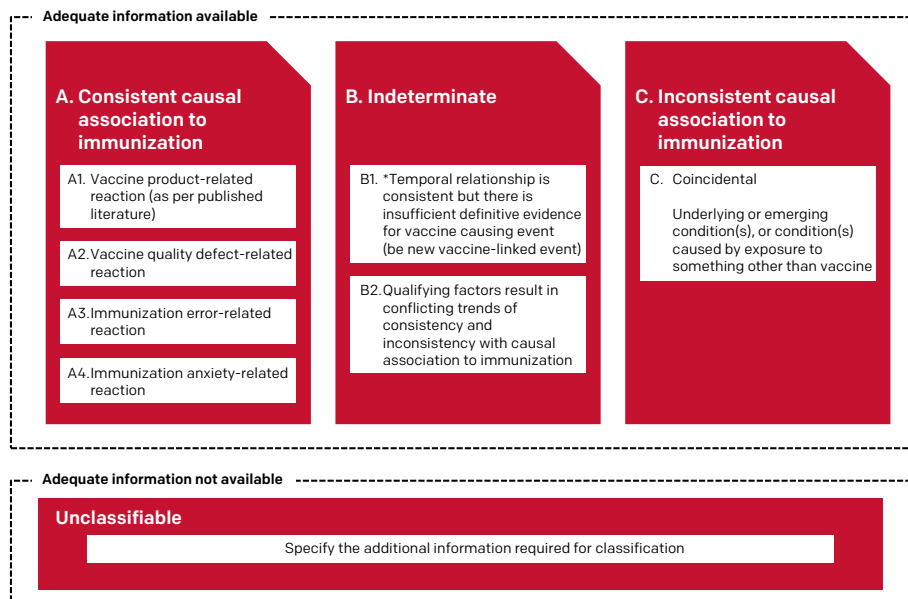
Case report form (CRF): A document that is used to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection. (WHO)

Causal association: A cause-and-effect relationship between a causative factor and a disease with no other factors intervening in the process. (WHO)

Causal factor: A factor that affects an event's outcome. Causal factor is not a root-cause. See *root-cause*.

Causality assessment: The systematic review of data about an AEFI case; aiming to determine the likelihood of a causal association between the event and the vaccine(s) received.

Causality assessment classification (modified from WHO)



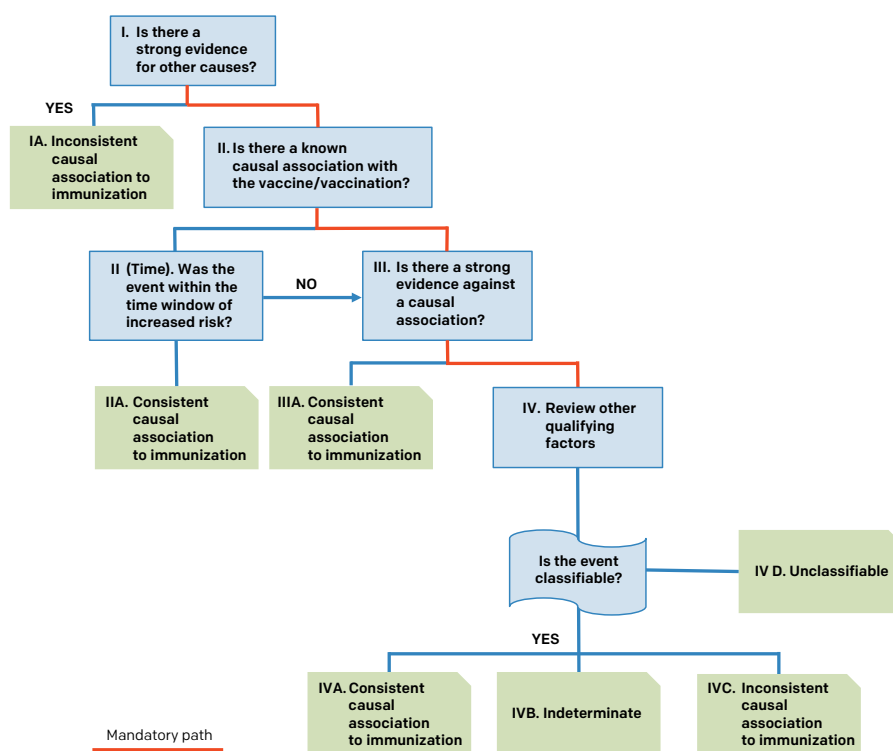
* B1: Potential signal and may be considered for investigation

The quality of the causality assessment depends upon:

- the performance of the AEFI reporting system in terms of responsiveness, effectiveness and quality of investigation and reports;
- the availability of adequate medical and laboratory services and access to background information
- the quality of the causality review process.

Causality assessment usually will not prove or disprove an association between an event and the immunization. It is meant to assist in determining the level of certainty of such an association. A definite causal association or absence of association often cannot be established for an individual event. (WHO)

Causality assessment algorithm (modified from WHO)



Cause: An antecedent set of actions, circumstances or conditions that produce an event, effect, or phenomenon. A cause may be proximate (immediately precede) or remote (a factor in predisposing to) the event, effect, or phenomenon. (*Canadian Patient Safety Dictionary*)

Cause and effect diagrams: See *fish bone diagram* and *fault-tree analysis*.

Center of Excellence for Independent Validators in Pharmaceutical Logistics

(CEIV): An IATA project to help organizations and the entire air cargo supply chain to get on the right track to achieve pharmaceutical handling excellence. CEIV Pharma addresses industry's need for more safety, security, compliance and efficiency to create a globally consistent and recognized pharmaceutical product handling certification. By establishing a common baseline from existing regulations and standards, this certification ensures international and national compliance to safeguard product integrity while addressing specific air cargo needs.

CEIV Pharma encompasses, or even supersedes, many of the existing pharmaceutical standards and guidelines such as:

- IATA Temperature Control Regulations (TCR)
- European Union Good Distribution Practices (EU GDP)
- World Health Organization (Annex 5 of TRS 957)
- United States Pharmacopeia Standards

Change management: A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (*ICH Q10*)

Change management system: A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system. As defined by the ICH Q10, the change management system should include the following, as appropriate for the stage of the lifecycle:

1. Quality risk management should be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk;
2. Proposed changes should be evaluated relative to the marketing authorisation, including design space, where established, and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. As stated in ICH Q8 Pharmaceutical Development, working within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system standpoint, all changes should be evaluated by a company's change management system;
3. Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., pharmaceutical development, manufacturing, quality, regulatory affairs and medical), to en-

sure the change is technically justified. Prospective evaluation criteria for a proposed change should be set;

- 4. After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.

Application of change management system throughout the product lifecycle (ICH Q10)

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk based assessments.	Any changes after product discontinuation should go through an appropriate change management system.

Charter: A document prepared by the sponsor, which establishes the role and responsibilities of the DSMB vis-à-vis the sponsor and other parties engaged in the study. (WHO)



LIMITmarker™ F-A from Temptime Corp.
+9°C (±1°C) threshold indicator



FREEZEmarker™ L from Temptime Corp.
0.0°C (±1°C) threshold indicator

Examples of chemical indicators (Temptime Corp.)

Chemical indicators: (also called markers or phase-change indicators), are generally impregnated onto a paperboard substrate. These indicators, sometimes referred to as critical temperature indicators, are based on a phase change or chemical reaction that occurs as a function of temperature. Examples include liquid crystals, waxes, polymers, and lacquers that change phase, and thereby their appearance, as a function of temperature. Chemical temperature threshold indicators are irreversible and are suitable for high or low temperatures. Temperature threshold indicators show a response and typically are single-use devices. These indicators provide a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature. (WHO)

Chlorofluorocarbons (CFCs): A CFC is an organic compound that contains only carbon, chlorine, and fluorine, produced as a substituted derivative of methane and ethane. It is an ozone-depleting compound, which is highly damaging to the environment. It is now illegal to operate refrigerated vehicles using CFCs as the refrigerating fluid or to have CFCs within the insulation in non-Article 5 countries. WHO recommends that fixed refrigeration equipment and refrigerated vehicles containing CFC's should not be purchased or operated. (*WHO*)

Class A packaging: Prior to - and at the time of packing - the vaccines must be kept within the storage temperature limits recommended by the manufacturer. The vaccine must be packed to ensure that the warmest temperature inside the insulated package does not rise above +8°C in continuous outside ambient temperatures of +43°C for a period of at least 48 hours (*WHO*). See also *class ABC packaging*.

Class ABC packaging: On the basis of their thermostability and presentation, WHO classifies the vaccines into three categories (A, B and C) for packaging of international shipments. WHO specifies the minimum and maximum acceptable temperatures to which vaccines in each category can be exposed during international transport, for a period of at least 48 hours. See also *class A packaging*, *class B packaging* and *class C packaging*.

WHO classification and temperature criteria for international shipment of vaccines

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	DT DTP DTP-HepB DTP-Hib (liquid) DT IPV HepB HPV Hib (liquid) pneumococcal	+43°C	+2°C	+30°C
	Td TT	-5°C	+2°C	+30°C

Class B packaging: Prior to - and at the time of packing - the vaccines must be kept within the storage temperature limits recommended by the manufacturer. The vaccines must be packed to ensure that the warmest temperature inside the insulated package does not rise above +30°C in continuous outside ambient temperatures of +43°C for a period of at least 48 hours. Diluents for freeze-dried vaccines must always be included with the vaccine shipment in a quantity that matches the quantity of vaccine; diluents, however, do not require temperature-controlled packaging (WHO). See also *class ABC packaging*.

Class C packaging: Prior to - and at the time of packing - the vaccines must be kept within the storage temperature limits recommended by the manufacturer. The vaccines must be packed to ensure that the warmest temperature inside the insulated package does not rise above +30°C in continuous outside ambient temperatures of +43°C for a period of at least 48 hours; and the coolest storage temperature of the vaccine does not fall below +2°C in continuous external temperatures of -5°C for a period of at least 48 hours (WHO). See also *class ABC packaging*.

Client: The organization or individual that is responsible for procuring a building development; sometimes referred to as the *employer*. (WHO)

Climate zone (for refrigerators): The highest constant ambient temperature at which a WHO prequalified vaccine refrigerator can maintain the vaccine storage compartment between +2°C and +8°C. Established during laboratory testing. (WHO) The three PQS climate zones are:

- Temperate (up to +27°C)
- Moderate (up to +32°C)
- Hot (up to +43°C)

Also see *temperature zone symbols for refrigerators*.

Climatic zone: The zones into which the world is divided based on the prevailing annual climatic conditions. In order to be able to reduce the amount of stability testing required, the number of different long-term testing conditions must be reduced to a sufficient extent (WHO). Four different long-term testing conditions are defined, which match with the climatic conditions of the target markets categorized in just four different climatic zones. This concept is described in regulatory guidelines and pharmacopoeias and has become an established standard in developing finished pharmaceutical products (FPPs).

At the 40th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations held in Geneva in October 2005 (4), it was recommended to split the current Climatic Zone IV (hot and humid) into two zones: Climatic Zone IVA – for which 30°C/65% RH will remain the standard long-term testing condition – and Climatic Zone IVB for which, if justified, 30°C/75% RH will become the long-term testing condition.

Proposed criteria and long-term testing conditions (WHO)

Climatic zone	Definition	Criteria Mean annual temperature measured in the open air/ mean annual partial water vapour pressure	Long-term testing conditions
I	Temperate climate	=< 15°C / =< 11 hPa	21°C / 45% RH
II	Subtropical and Mediterranean climate	> 15°C / > 11 to 18 hPa	25°C / 60% RH
III	Hot and dry climate	> 22°C / =< 15 hPa	30°C / 35% RH
IVA	Hot and humid climate	> 22°C / > 15 to 27 hPa	30°C / 65% RH
IVB	Hot and very humid climate	> 22°C / > 27 hPa	30°C / 75% RH

Additional testing conditions i.e., accelerated and – if applicable – intermediate conditions have to be used as described in these guidelines. Selection of the conditions for stability testing is based on a risk analysis. Testing at a more severe long-term condition can be an alternative to storage testing at 25°C/60% RH or 30°C/65% RH. The evaluation of the climatic conditions by each WHO Member State resulted in the recommended storage condition for long-term stability studies shown in the below Table (in some of the countries listed, more extreme conditions are also accepted). The list is grouped by WHO regional offices.

Stability conditions for WHO Member States by Region

Member State	Stability conditions Confirmed long-term testing condition
<i>Regional Office for Africa (AFRO)</i>	
Algeria	[25°C/60% RH] ³
Angola	[30°C/65% RH] ³
Benin	[30°C/65% RH] ³
Botswana	30°C/50% RH ¹
Burkina Faso	30°C/60% RH ²
Burundi	[30°C/65% RH] ³
Cameroon	30°C/75% RH ²
Cape Verde	[30°C/65% RH] ³
Central African Republic	30°C/75% RH ²
Chad	[30°C/65% RH] ³

Member State	Stability conditions Confirmed long-term testing condition
Comoros	[30°C/65% RH] ³
Congo	[30°C/65% RH] ³
Côte d'Ivoire	[30°C/65% RH] ³
Democratic Republic of the Congo	[30°C/65% RH] ³
Equatorial Guinea	[30°C/65% RH] ³
Eritrea	[30°C/65% RH] ³
Ethiopia	[30°C/65% RH] ³
Gabon	[30°C/65% RH] ³
Gambia	30°C/65% RH¹
Ghana	30°C/75% RH ²
Guinea	[30°C/65% RH] ³
Guinea-Bissau	[30°C/65% RH] ³
Kenya	[30°C/65% RH] ³
Lesotho	30°C/75% RH ²
<i>Liberia</i>	[30°C/65% RH] ³
Madagascar	30°C/65% RH¹
Malawi	[25°C/60% RH] ²
Mali	[30°C/65% RH] ³
Mauritania	[30°C/65% RH] ³
Mauritius	[30°C/65% RH] ³
Mozambique	30°C/75% RH¹
Namibia	30°C/65% RH¹
Niger	[30°C/65% RH] ³
Nigeria	30°C/75% RH ²
Rwanda	[30°C/65% RH] ³
Sao Tome and Principe	30°C/75% RH ²
Senegal	[30°C/65% RH] ³
Seychelles	[30°C/65% RH] ³
Sierra Leone	30°C/75% RH ²
South Africa	30°C/65% RH¹
Swaziland	[25°C/60% RH] ³
Togo	30°C/75% RH ²
Uganda	30°C/65% RH¹
United Republic of Tanzania	30°C/75% RH ²
Zambia	30°C/65% RH¹
Zimbabwe	30°C/75% RH ²

Member State	Stability conditions Confirmed long-term testing condition
Regional Office for the Americas (AMRO)	
Antigua and Barbuda	[30°C/75% RH] ³
Argentina	25°C/60% RH ²
Bahamas	[30°C/65% RH] ³
Barbados	30°C/75% RH ²
Belize	[30°C/65% RH] ³
Bolivia	[30°C/70% RH or 30°C/75% RH] ³
Brazil	30°C/75% RH¹
Canada	25°C/60% RH or 30°C/65% RH¹
Colombia	[30°C/65% RH] ³
Costa Rica	30°C/75% RH ²
Cuba	30°C/75% RH ²
Dominica	[30°C/65% RH] ³
Dominican Republic	[30°C/65% RH] ³
Ecuador	[30°C/65% RH] ³
El Salvador	[30°C/65% RH] ³
Grenada	[30°C/65% RH] ³
Guatemala	[30°C/65% RH] ³
Guyana	[30°C/70% RH or 30°C/75% RH] ³
Haiti	[30°C/65% RH] ³
Honduras	[30°C/65% RH] ³
Jamaica	[30°C/65% RH] ³
Mexico	[25°C/60% RH] ³
Nicaragua	[30°C/65% RH] ³
Panama	[30°C/75% RH] ³
Paraguay	[30°C/65% RH] ³
Peru	[30°C/75% RH]¹
Saint Kitts and Nevis	[30°C/65% RH] ³
Saint Lucia	30°C/65% RH ²
Saint Vincent and the Grenadines	[30°C/75% RH] ³
Suriname	[30°C/70% RH or 30°C/75% RH] ³
Trinidad and Tobago	[30°C/65% RH] ³
United States of America	25°C/60% RH or 30°C/65% RH¹
Uruguay	[25°C/60% RH] ³
Venezuela (Bolivarian Republic of)	[30°C/70% RH or 30°C/75% RH] ³

Member State	Stability conditions Confirmed long-term testing condition
Regional Office for the Eastern Mediterranean (EMRO)	
Afghanistan	30°C/65% RH ¹
Bahrain	30°C/65% RH ¹
Djibouti	30°C/65% RH ¹
Egypt	30°C/65% RH ¹
Iran (Islamic Republic of)	30°C/65% RH ¹
Iraq	30°C/65% RH ¹
Jordan	30°C/65% RH ¹
Kuwait	30°C/65% RH ¹
Lebanon	25°C/65% RH ¹
Libyan Arab Jamahiriya	25°C/65% RH ¹
Morocco	25°C/65% RH ¹
Oman	30°C/65% RH ¹
Pakistan	30°C/65% RH ¹
Qatar	30°C/65% RH ¹
Saudi Arabia	30°C/65% RH ¹
Somalia	30°C/65% RH ¹
Sudan	30°C/65% RH ¹
Syrian Arab Republic	25°C/65% RH ¹
Tunisia	25°C/65% RH ¹
United Arab Emirates	30°C/65% RH ¹
Yemen	30°C/65% RH ¹
Regional Office for Europe (EURO)	
Albania	[25°C/60% RH] ³
Andorra	[25°C/60% RH] ³
Armenia	[25°C/60% RH] ³
Austria	25°C/60% RH or 30°C/65% RH ¹
Azerbaijan	30°C/65% RH ²
Belarus	[25°C/60% RH] ³
Belgium	25°C/60% RH or 30°C/65% RH ¹
Bosnia and Herzegovina	[25°C/60% RH] ³
Bulgaria	25°C/60% RH or 30°C/65% RH ¹
Croatia	[25°C/60% RH] ³
Cyprus	25°C/60% RH or 30°C/65% RH ¹
Czech Republic	25°C/60% RH or 30°C/65% RH ¹
Denmark	25°C/60% RH or 30°C/65% RH ¹

Member State	Stability conditions Confirmed long-term testing condition
Estonia	25°C/60% RH or 30°C/65% RH ¹
Finland	25°C/60% RH or 30°C/65% RH ¹
France	25°C/60% RH or 30°C/65% RH ¹
Georgia	[25°C/60% RH] ³
Germany	25°C/60% RH or 30°C/65% RH ¹
Greece	25°C/60% RH or 30°C/65% RH ¹
Hungary	25°C/60% RH or 30°C/65% RH ¹
Iceland	[25°C/60% RH] ³
Ireland	25°C/60% RH or 30°C/65% RH ¹
Israel	30°C/70% RH or 30°C/75% RH ¹
Italy	25°C/60% RH or 30°C/65% RH ¹
Kazakhstan	[25°C/60% RH] ³
Kyrgyzstan	[25°C/60% RH] ³
Latvia	25°C/60% RH or 30°C/65% RH ¹
Lithuania	25°C/60% RH or 30°C/65% RH ¹
Luxembourg	25°C/60% RH or 30°C/65% RH ¹
Malta	25°C/60% RH or 30°C/65% RH ¹
Monaco	25°C/60% RH or 30°C/65% RH ²
Montenegro	[25°C/60% RH] ³
Netherlands	25 °C/60% RH or 30 °C/65% RH ¹
Norway	[25°C/60% RH] ³
Poland	25°C/60% RH or 30°C/65% RH ¹
Portugal	25°C/60% RH or 30°C/65% RH ¹
Republic of Moldova	[25°C/60% RH] ³
Romania	25°C/60% RH or 30°C/65% RH ¹
Russian Federation	[25°C/60% RH] ³
San Marino	[25°C/60% RH] ³
Serbia	[25°C/60% RH] ³
Slovakia	25°C/60% RH or 30°C/65% RH ¹
Slovenia	25°C/60% RH or 30°C/65% RH ¹
Spain	25°C/60% RH or 30°C/65% RH ¹
Sweden	25°C/60% RH or 30°C/65% RH ¹
Switzerland	25°C/60% RH or 30°C/65% RH ¹
Tajikistan	[25°C/60% RH] ³
The former Yugoslav Republic of Macedonia	25°C/60% RH or 30°C/65% RH ²
Turkey	[25°C/60% RH] ³

Member State	Stability conditions Confirmed long-term testing condition
Turkmenistan	[25°C/60% RH] ³
Ukraine	[25°C/60% RH] ³
United Kingdom	25°C/60% RH or 30°C/65% RH ¹
Uzbekistan	[25°C/60% RH] ³
Regional Office for South-East Asia (SEARO)	
Bangladesh	[30°C/65% RH] ³
Bhutan	30°C/65% RH ²
Democratic People's Republic of Korea	[25°C/60% RH] ³
India	30°C/70% RH ¹
Indonesia	30°C/75% RH ¹
Maldives	[30°C/65% RH] ³
Myanmar	30°C/75% RH ¹
Nepal	30°C/75% RH ²
Sri Lanka	[30°C/65% RH] ³
Thailand	30°C/75% RH ¹
Timor-Leste	[30°C/65% RH] ³
Regional Office for the Western Pacific (WPRO)	
Australia	25°C/60% RH or 30°C/65% RH ²
Brunei Darussalam	30°C/75% RH ¹
Cambodia	30°C/75% RH ¹
China	[30°C/65% RH] ³
Cook Islands	[30°C/65% RH] ³
Fiji	[30°C/65% RH] ³
Japan	25°C/60% RH or 30°C/65% RH ¹
Kiribati	[30°C/65% RH] ³
Lao People's Democratic Republic	30°C/75% RH ¹
Malaysia	30°C/75% RH ¹
Marshall Islands	[30°C/65% RH] ³
Micronesia (Federated States of)	[30°C/65% RH] ³
Mongolia	[25°C/60% RH] ³
Nauru	[30°C/65% RH] ³
New Zealand	25°C/60% RH or 30°C/65% RH ¹
Niue	[30°C/65% RH] ³
Palau	[30°C/65% RH] ³
Philippines	30°C/75% RH ¹
Papua New Guinea	[30°C/65% RH] ³

Member State	Stability conditions Confirmed long-term testing condition
Republic of Korea	25°C/60% RH or 30°C/65% RH ²
Samoa	[30°C/65% RH] ³
Singapore	30°C/75% RH ¹
Solomon Islands	[30°C/65% RH] ³
Tonga	[30°C/65% RH] ³
Tuvalu	[30°C/65% RH] ³
Vanuatu	[30°C/65% RH] ³
Viet Nam	30°C/75% RH ¹

¹ Information obtained through respective regional harmonization groups (e.g., ASEAN, ICH and GCC) and from official communications from national medicines regulatory authorities to WHO [entries in bold type].

² Information collated during the 13th International Conference of Drug Regulatory Authorities (IC-DRA), 16–18 September 2008, held in Berne Switzerland, from representatives of national medicines regulatory authorities [entries in normal type].

³ Information provided by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) [entries in italic type].

Clinical trial/study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous. (*ICH E6/R1*)

Clinical trials involving new medicinal products are commonly classified into four phases. Each phase is treated as a separate clinical trial. When the investigational product successfully passes through phases 0, 1, 2 and 3, it is approved by the national regulatory authority for use.

Phases of clinical trials

Phase	Objective	Notes
Phase 0	<ul style="list-style-type: none"> ■ To establish whether the agent behaves in humans as was expected from preclinical animal studies, ■ To gather preliminary data on pharmacodynamics or pharmacokinetics, ■ To select promising lead candidates, or to explore biodistribution characteristics. 	Developed in response to the US FDA's recent exploratory Investigational New Drug (IND) guidance. Officially named at the FDA as an exploratory investigational new drug study and also known as a "micro-dosing" study. Phase 0 studies do not replace formal Phase I drug safety testing and do not offer any possibility of patient benefit. In these trials, a very small dose of a drug is given to about 10 to 15 people.

Phase	Objective	Notes
Phase 1	<ul style="list-style-type: none"> ■ To evaluate how the drug is metabolized and excreted ■ To evaluate safety including safe dosage range and identifying side effects 	Testing within a small group of healthy volunteers, typically ranging from 20 to 80 to evaluate how the drug is metabolized and excreted, its safety, determine safe dosage ranges, and begin to identify side effects. A drug's side effects could be subtle or long term, or may only happen with a few of people, so phase 1 trials are not expected to identify all side effects.
Phase 2	<ul style="list-style-type: none"> ■ To determine efficacy ■ To further evaluate safety 	Phase 2 studies begin if Phase 1 studies do not reveal unacceptable toxicity. Testing with a larger group of people (100–300) to see if it is effective and to further evaluate its safety. The gradual increase in test group size allows less-common side effects to be progressively sought.
Phase 3	<ul style="list-style-type: none"> ■ To monitor adverse events ■ Final confirmation of safety and efficacy 	Testing with large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely. Phase three research is the clinical trial, in which the drug is administered to a large number of patients and compared to another drug if there is one for the condition in question (if not to a placebo). Where possible, such trials are “double-blinded”, i.e., neither research subjects nor their physicians know who is receiving which drug or placebo.
Phase 4	Post-marketing surveillance	Post-marketing studies delineate additional information, including the treatment's risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use.

Clinical trials registry: An official platform and catalogue for registering a clinical trial. Some countries require clinical trials being conducted in that country to be registered, others do not. The goal of clinical trials registry is to provide transparency and access to clinical trials, made available to the public.

Cluster: Two or more cases of the same event or similar events related in time, geography, and/or the vaccine administered. (*WHO*)

Cluster sampling: A sampling methodology that involves: dividing the population into subgroups or clusters that are not necessarily (and preferably not) homogeneous; draw-

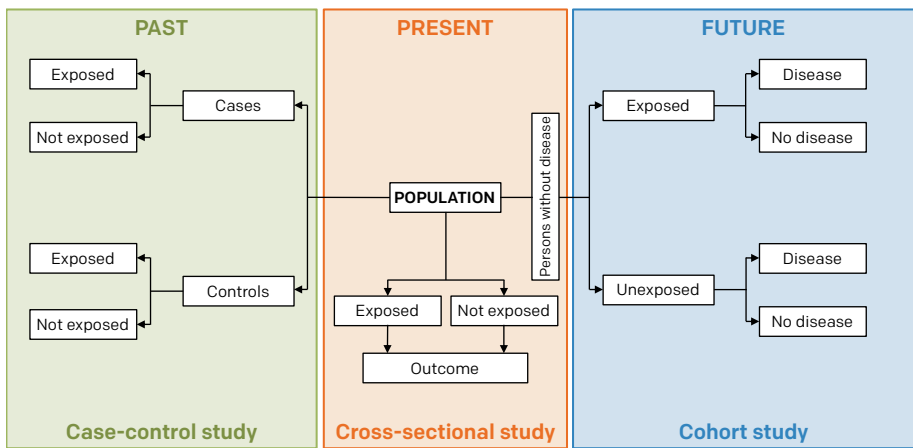
ing a random sample of the clusters; and selecting all or a random sample of the persons in each cluster. When each cluster comprises persons in a localized geographic area, such as a county, cluster sampling is especially useful for national surveys. (WHO)

Coefficient of heat transfer: (The "U" value, also referred to as the "K" coefficient in the ATP Agreement) The overall heat transfer of the equipment, defined as the heating power or cooling capacity, W, per degree temperature difference, T, between the internal and external surfaces over the surface of the body, S. (WHO)
The units are W/(m²K) and its formula is below.

$$K = \frac{W}{S \times \Delta T}$$

Cohort study: A form of longitudinal study used in various fields including medicine. In medicine, it is an analysis of risk factors and follows a group of people who do not have the disease, and uses correlations to determine the absolute risk of subject contraction. Cohort studies are largely about the life histories of segments of populations, and the individual people who constitute these segments.

Design of a cohort study in comparison with cross-sectional and case-control studies (Kartoglu)



Coincidental event: An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety. (WHO)

Cold: The condition or subjective perception of having low temperature. Though some define cold as the "absence of heat" it is not fully correct since temperature re-

Vaccine Cold Chain Monitor				
Date in	Index	Location	Date out	Index

3M MasterMark™			
IF A all Blue	IF B all Blue	IF C all Blue	IF A & B & C all Blue
Use within 2 months	Use within 2 months	Use within 2 months	TEST VACCINE BEFORE USE
These vaccines may be used			

SUPPLIER FOURNISSEUR	Name: _____ Name: _____ Date of allocation: _____ Date of expiration: _____ Vaccine: _____ Vaccine: _____
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Cold chain monitor card (PQS code E006/004)

lates to the thermal energy held by an object, which is the kinetic energy of the random motion of particle constituents of the object, an object will have less thermal energy when it is colder. Absence of heat is only possible at the "absolute zero" point at -273.15°C (zero kelvin) where all motion of the particles are ceased and completely at a resting state.

Cold chain: The entire chain of storage facilities and transportation links through which supplies move from manufacturer to consumer, including port facilities, the primary store, intermediate stores, all service delivery points, equipment and transport vehicles. (WHO)

Cold chain monitor (CCM): WHO no longer recommends the use of these cards for in-country use.

Their use should now be confined to international shipments only, where dry ice is used; otherwise electronic shipping indicators are generally preferred for this purpose. (WHO)

Cold life: Cold life is measured from the moment when the container lid is closed until the temperature of the warmest point in the vaccine storage compartment first reaches $+10^{\circ}\text{C}$, at a constant ambient temperature of $+43^{\circ}\text{C}$. Cold life applies when fully frozen water-packs are used as the coolant; these will continue to be used for transporting OPV and single antigen freeze-dried (lyophilized) vaccines. (WHO)



Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b combined vaccine from Serum Institute of India Ltd.

(10 dose vial liquid DTwP-HepB + 10 dose vial lyophilised Hib)

Cold room: A purpose made insulated enclosure fitted with refrigeration equipment which maintains a set temperature above 0°C . (WHO)

Cold store: A facility where the cold room/freezer room or other refrigeration equipment are located, including a packaging area. (WHO)

Combined vaccine: A vaccine that consists of two or more antigens, combined by the manufacturer at the final formulation stage or mixed immediately before administration. Such vaccines are intended to protect against either more than one disease, or against one disease caused by different strains or serotypes of the same organism. (WHO)

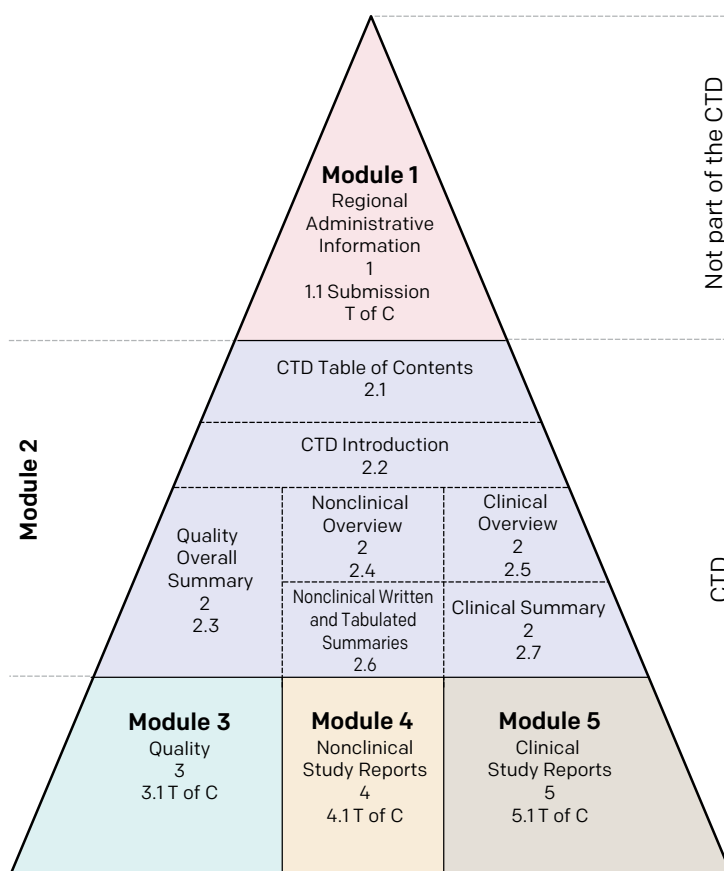
Commitment batches: Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application. (WHO)

Commodities: Used interchangeably with stock, goods, products, supplies, and other terms in this manual to refer to all the items that flow through a supply system. (WHO)

Common carrier: A seller of distribution services.

Common technical document (CTD): A set of ICH specification for application dossier for the registration of medicines. The CTD is organized into five modules; Module 1 is region specific and Modules 2-5 are intended to be common for all regions.

Diagrammatic representation of the organization of the ICH Common Technical Document



Community: A community is a group of people understood as having a certain identity due to the sharing of common interests or to a shared proximity. A community may be identified as a group of people living in the same village, town, or country and, thus, sharing geographical proximity. A community may be otherwise identified as a group of people sharing a common set of values, a common set of interests, or a common disease. (WHO)

Community investigation: A population-based trial in large predefined segments of the population to investigate the impact of a treatment on a preventable infectious disease. (WHO)

Commutability: In general terms the concept of commutability seeks to establish the extent to which the reference standard is suitable to serve as a standard for the variety of samples being assayed. The way in which this is done may vary according to the intended application. (WHO)

Comparator product: An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial (ICH E6/R1). The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. The selection of the comparator product is usually made at the national level by the medicines regulatory authority. See elsewhere for guidance on how to deal with the situation where the comparator proves, on testing, to be of poor quality, e.g., it has poor bio-availability.

Complaint: An expression of dissatisfaction with a product or service and is filed by a customer and received by an organization.

Component: Any major piece, part or assembly of the main equipment or sub-equipment that does not have its own power supply and could not operate as a stand-alone unit (e.g., valves and switches). (WHO)

Compression cycle refrigerator: Refrigerator that uses an electrically powered compressor to drive the cooling system. The electrical supply may come from the grid, a generator or from a renewable source such as solar energy, with or without a battery pack. Provides more reliable and energy-efficient cooling than an absorption cycle refrigerator. (WHO)

Conditioning: Exposing an object to a desired temperature environment to bring its state or situation to a situation with respect to circumstances. Placing water-packs in a freezer to produce ice-packs is a conditioning process. Conditioning is complet-

ed when the object reaches thermal equilibrium with the environment it is exposed to. WHO uses the term “conditioning” for frozen icepacks being exposed to room temperature until there is some liquid water in the container, meaning that the ice has reached its phase change point and is at its latent phase.

Conduction: Transfer of heat occurring at molecular level through contact. Some solids, such as metals, are good conductors of heat while others, such as wood, are poor conductors. This is why when one touches a metal and a wooden spoon, metal spoon would feel colder (even though they are at same temperature) because of the high conductivity.



Bakelite handle helps to reduce conduction type heat transfer
(Pollapat Chirawong, Shutterstock)

Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor’s proprietary information or of a subject’s identity. (ICH E6/R1)

Conflict of interest: A situation in which a person or organization is involved in financial, emotional or other type interests, one of which could possibly jeopardize his/her (their) ability to provide free and independent advice. Conflict of interest is not declaring a “wrong doing”; it is a situation that many at a time we all fall in. This does not make one act unprofessionally. Many committee members in organizations have to make declaration of their interest. Such declarations are also common for authors in peer-review journals. These declarations are made public so the organization, attendees of meetings as well as readers of peer-review journals are aware of the situation.

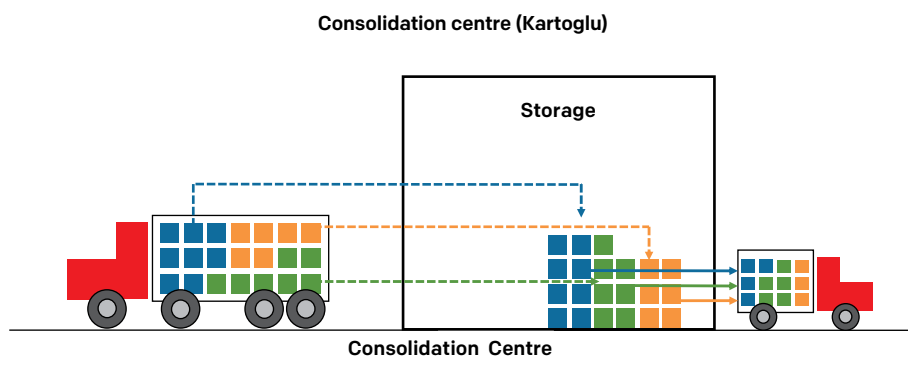
Conformity: The fulfilment of a requirement. Requirements may include customer requirements, quality requirements, quality management requirements, management requirements, product requirements, service requirements, contractual requirements, statutory requirements, and regulatory requirements.

Conjugated vaccine: A vaccine produced by covalently binding an antigen to a carrier protein with the intention of improving the immunogenicity of the attached antigen. This technique is most often applied to bacterial polysaccharides for the prevention of invasive bacterial disease.



Pneumococcal 7-valent Conjugate Vaccine - Prevnar: Diphtheria CRM197 Protein manufactured by Pfizer/Wyeth

Consolidation centre: A warehouse where multiple products are held so orders can be picked for onward delivery to customers. In a typical immunization supply chain the primary and intermediate storage facilities are consolidation centre type warehouses. (WHO)



Constitution: A constitution sets forth fundamental principles about how a particular entity is constituted and governed. Most governmental systems have constitutions, as do some international organizations (including the WHO) and private associations. Constitutions authorize the entity to engage in particular actions and may also establish specific limits on the entity's use of its powers.

Governmental constitutions typically include provisions establishing the law-making process, allocating responsibility among governmental actors, and protecting individual liberties and minority rights. Most governmental constitutions are codified - i.e., they are assembled into a single, organized system of written rules. (WHO)

Consumption records: Records kept on products consumed. See also *stock keeping records* and *transaction records*.

Contact: An individual who has had contact with an infected person (case) in a way that is considered as having caused significant exposure and therefore a risk of infection. (WHO)

Container closure system: The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the FPP. A packaging system is equivalent to a container closure system. (WHO)



A primary container closure system with flip off, aluminum crimping and rubber stopper (Kartoglu)

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport. (*ICH Q7A*)

Continuous process validation: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (*ICH Q8/R2*)

Contract: A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract. (*ICH E6/R1*)

Contract manufacturer: A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer. (*WHO*)

Contract research organization (CRO): A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions. (*ICH E6/R1*)

Contributing cause: A factor, situation, or agent that accelerates or intensifies the occurrence of the unwanted event. If the contributing cause is removed, it does not prevent the unwanted event from occurring. (*J Vesper*)

Contributing factors: The reason(s), situational factor(s), or latent condition(s) that played a role in the genesis of an adverse outcome. (*Canadian Patient Safety Dictionary*)

Control: Any comparator suitable for validation of the trial. The comparator may be either an active treatment or a placebo control. (*WHO*)

Control (of disease): The reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction. Example: The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPD) by WHO/UNICEF.

Control strategy: A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (*ICH Q10*)

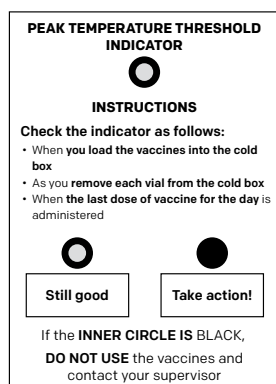
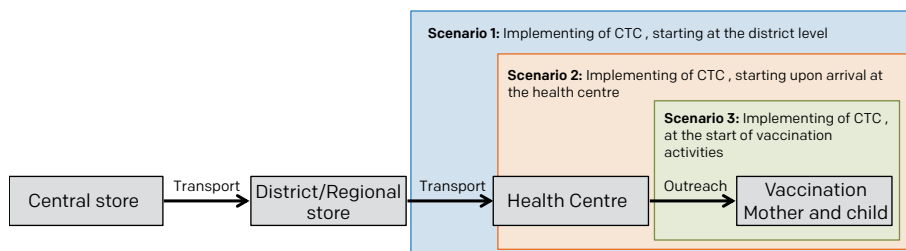
Controlled or hazardous products: TTSPPs and other products with high illicit value: poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials. (WHO)

Controlled temperature chain (CTC): An innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen. A CTC typically involves a single excursion of the vaccine into ambient temperatures not exceeding +40°C and for duration of a specific number of days, just prior to administration. (WHO)

The WHO has established the following programmatic criteria for a vaccine to be labelled for and used in a CTC:

1. The vaccine should be used in a campaign or special strategy setting. CTC is not currently recommended for immunization through routine delivery.
2. The vaccine must be able to tolerate ambient temperatures of at least +40°C for a minimum of three days and should be accompanied by:
 - a. a vaccine vial monitor (VVM) on each vial, and
 - b. a peak threshold indicator in each vaccine carrier.
3. The vaccine must be licensed for use in a CTC by the relevant regulatory authorities, with a label that specifies the conditions.

Possible scenarios for implementation of CTC as defined by WHO (Kartoglu)



CTC was integrated into Meningococcal A conjugate vaccine mass preventive campaigns for the first time in three West African countries in 2014.

For details on the CTC policy, see <http://goo.gl/G78crJ>

Peak threshold temperature indicator used in CTC (Temptime Corp.)

Controller: A device that interprets a mechanical, digital or analogue signal, by a sensor, to control an equipment or component. (WHO)

Controller, critical: A controller for which control has a direct impact on the quality of the product or proper operation of the equipment. (WHO)

Controller, non-critical: A controller for which control has no direct impact on the quality of the product or proper operation of the equipment. (WHO)

Convection: Transfer of heat from one place to another by the movement of fluids and air. Convection is the circular motion that happens when warmer air or liquid which has faster moving molecules, making it less dense rises, while the cooler air or liquid drops down.



Convection in a pot over gas stove (Roman Sigaev, Shutterstock)

Cool: Fairly low temperature.

Cool down time: The time required for a WHO pre-qualified vaccine refrigerator to cool down to within the acceptable temperature range of $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$, measured from the moment when the appliance is initially turned on. Established by laboratory testing at the ambient temperature of the climate zone for which the appliance is prequalified. (WHO)

Cool life: Cool life with cool water-packs at $+5^{\circ}\text{C}$: Cool life is measured from the moment when the container is closed, until the temperature of the warmest point inside the vaccine storage compartment first reaches $+20^{\circ}\text{C}$, at a constant ambient temperature of $+43^{\circ}\text{C}$. Cool life applies when cool water-packs are used. (WHO)

Cool life test: The empty passive container is stabilized at $+43.0^{\circ}\text{C}$ and loaded with cool water-packs which have been stabilized at $+5.0^{\circ}\text{C}$ for a minimum of 24 hours. Cool life is measured from the moment when the container is closed, until the temperature of the warmest point inside the storage compartment first reaches $+20.0^{\circ}\text{C}$, at a constant ambient temperature of $+43.0^{\circ}\text{C}$. (WHO)

Cool water-pack: A water-pack cooled to a temperature of between $+2.0^{\circ}\text{C}$ and $+8^{\circ}\text{C}$ before use. (WHO)

The only way to eliminate the freezing risk entirely is to transport liquid vaccines, other than OPV, in cold boxes lined with cool water-packs which have been precooled in a refrigerator to a temperature of $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$. Where it is essential to transport OPV, liquid and freeze-dried vaccines in a single carrier, experiments have shown that

cool water-packs may safely be used provided the cool life of the carrier is not exceeded. Changing over to the use of cool water-packs involves significant changes in practice. In addition there are equipment implications because additional refrigerators will be needed at primary and sub-national level to cool the water-packs in bulk.

Coolant: Ice, water, water-based gel, phase-change material, dry ice, or other substance, typically encapsulated in a rigid or flexible plastic container, used to maintain a predefined temperature range inside a passive container during transport operations. (*WHO*)

Cooling: The process of removing heat from a system by exposing it to an environment (or another system) that is at lower temperature. Cooling occurs through the transfer of thermal energy through radiation, convection and conduction.

Coordinating investigator: An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial. (*ICH E6/R1*)

Correction: A correction is any action that is taken to eliminate nonconformity or other undesirable situation. However, corrections do not address root causes. When applied to products, corrections can include reworking products, reprocessing them, regrading them, assigning them to a different use, or simply destroying them.

Corrective action: Action to eliminate the cause of a detected nonconformity or other undesirable situation. Corrective action is taken to prevent recurrence. (*ISO 9001:2015*)

Cost benefit analysis: A conceptual framework applied to any systematic, quantitative appraisal of a public or private project to determine whether, or to what extent, that project is worthwhile from a social perspective. Cost-benefit analysis differs from a straightforward financial appraisal in that it considers all gains (benefits) and losses (costs) to social agents. Cost benefit analysis usually implies the use of accounting prices. (*EU*)

Cost effectiveness analysis: An appraisal and monitoring technique used when benefits cannot be reasonably measured in money terms. It is usually carried out by calculating the cost per unit of "non-monetised" benefit and is required to quantify benefits but not to attach a monetary price or economic value to the benefits. (*EU*)

Court decisions: Courts exist to hear criminal cases and to resolve disputes between private parties and challenges to governmental actions. In civil law countries (such as France), courts are required to decide all cases by reference to the published legal code. In common law countries (such as the United States), courts rely on the legal code if it

is applicable, but if no code provision applies they base their decision on “precedents,” or previous decisions in analogous cases decided by other judges. An important part of legal decision-making in common-law countries involves identifying relevant prior cases and determining how their reasoning applies to a current dispute. (WHO)

Critical control point (CCP): A step or procedure at which controls or checks can be applied to prevent or reduce a hazard or risk to an acceptable or critical level. In the context of distribution and handling of time- and temperature-sensitive pharmaceutical products, CCPs are typically defined for those activities where time and temperature abuse may occur or where critical processes that can affect the performance of the packaging solution or containment system are at risk. (WHO)

Critical deviation: A variation to previously established critical parameters or a significant variation to standard operations which could affect the quality of the API or intermediate. Critical deviations should always be investigated and corrective actions identified. (USFDA)

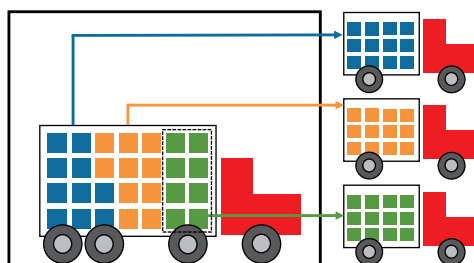
Critical process parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

Critical quality attribute (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8)

Cross-contamination: Contamination of a material or product with another material or product.

Cross-dock centre: There is no warehousing in cross-dock centres. In cross-dock centres, there is a direct transfer from incoming to outgoing vehicle without any storage taking place at all. (WHO)

Cross-dock centre (Kartoglu)



Cross-sectional study: A form of observational study carried out just one point in time or over a short period of time. Also known as transversal study or prevalence study. Associations found in cross-sectional studies are difficult to interpret.

Cryogenic dry/vapour shipper: A temperature-controlled insulated packaging container or system compatible with liquefied gases such as nitrogen used for maintaining extremely low temperatures during shipping. A porous medium internal to the shipping container absorbs and contains all the free flowing liquid and does not allow it to come into contact with the product - a process known as "charging". A fully charged and undamaged dry/vapour shipper containing nitrogen can maintain -196°C for up to 10 days, depending on the unit size. (WHO)

Cycle stock: See *working stock*.

D

Damage indicator: Go/no-go type indicators that can sense dropping or tipping during shipment and temperature tools that tell you whether shipments were exposed to extreme temperatures. Shock and tilt indicators are mounted on a packaging container, the device visually alerts both handlers and the recipient. They may be single use in different sensitivities or multi-use resettable intended for large crates and shipments weighing over 500 pounds. The contents of a package will always experience less impact than the package because of dampening characteristics of the package. Applying the shock indicator directly on products allows you to more accurately determine if an impact was damaging to the product. They are available in different g-force ranges. Shock and tilt indicators provide indisputable evidence of mishandling, and visually alert recipient to inspect contents before acceptance. Shock and tilt indicators are usually used for fragile, sensitive, perishable or calibrated goods. See also *impact indicator*, *shipping indicator*, and *g-force*.



Examples of shock and tilt indicators

Dangerous goods: Solids, liquids, or gases that can harm people, other living organisms, property, or the environment. Dangerous goods include materials that are radioactive, flammable, explosive, corrosive, oxidizing, asphyxiating, biohazardous,

toxic, pathogenic, or allergenic. Also included are physical conditions such as compressed gases and liquids or hot materials, including all goods containing such materials or chemicals, or may have other characteristics that render them hazardous in specific circumstances. Dangerous goods are often indicated by diamond-shaped signage on the material, container, or the building they are stored in. In many countries dangerous goods are known as hazardous materials (HAZMAT). Dangerous goods are divided into nine categories (and further down into some subcategories) on the basis of the specific chemical characteristics producing the risk:

1. Explosives
2. Gasses
3. Flammable liquids
4. Flammable solids
5. Oxidizing agents and organic peroxides
6. Toxic and infectious substances
7. Radioactive substances
8. Corrosive substances
9. Miscellaneous

Also see *Dangerous Goods Regulations* and *Hazard labels*.

Dangerous goods regulations (DGR): A reference to the industry to help preparing and documenting dangerous shipments. DGR manual is the global reference for shipping dangerous goods by air and the only standard recognized by airlines. As for the global regulation of the dangerous goods, many specialized organizations (e.g., IATA, ICAO, IMO, OTIF) has issued regulations specific to their sector, based on the “UN Recommendations on the Transport of Dangerous Goods” issued by the United Nations Economic and Social Council, which form the basis for most regional, national, and international regulatory schemes.

Data and safety monitoring board (DSMB): An independent committee established by the sponsor to assess, at intervals, the ongoing scientific and ethical integrity of a study by reviewing and evaluating (unblinded) data and reports at regular intervals. The DSMB provides non-bonding recommendations to the sponsor regarding study modification, suspension, or termination. There is no fixed or harmonized international name for committees performing this function. Other names for committees performing the same or similar functions include, but are not limited to: Data Monitoring Committee (DMC), Independent Data Monitoring Committee (IDMC), Monitoring Committee (MC), Data & Ethics Monitoring Committee (DEMC), Safety Monitoring Committee, Study Monitoring Committee. (WHO)

Dead space (in syringes): Space occupied by the hub and the needle such that after the delivery of a full dose of a vaccine the liquid in these sections is wasted. Dead space can be minimized both by incorporating a plastic neck of a needle that fits within the neck of a standard syringe hub and by using an extended plunger that inserts into the neck of the syringe. By doing so, the liquid that is expelled from the syringe is maximum.

Declaration of Helsinki (DoH): A set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA). Although DoH is not a legally binding document under the international law, it has been codified in or influenced both national and regional legislations and regulations throughout the world.

The declaration was originally adopted in June 1964 in Helsinki, Finland, and has since undergone seven revisions, most recently at the 64th WMA General Assembly in October 2013 in Fortaleza, Brazil. The current (2013) version is the only official one; all previous versions have been replaced and should not be used or cited except for historical purposes. For full text pdf version, please refer to <http://goo.gl/Kp2W2i>

The declaration is morally binding on physicians, and that obligation overrides any national or local laws or regulations, if the Declaration provides for a higher standard of protection of humans than the latter.

Decrees: Legally-binding announcements issued by the head of government. In the United States, decrees are known as “executive orders” and are issued directly by the President. Executive orders are directed to federal agencies, not to the public in general. For example, Presidents George Bush and Barack Obama both issued executive orders establishing rules for the use of federal funds to support embryonic stem cell research. (WHO)

Deductive reasoning: Examining a general situation in order to understand specific, individual cases. In this regard, deductive reasoning moves from the general to the specific and involves “backward thinking” to find out what actions, or conditions contributed to the examined unwanted event. “What caused it to happen?” or “How did it happen?” is the major question in deductive reasoning. FTA risk assessment tool uses deductive reasoning.

Defects per million opportunities (DPMO): A measure of process performance used in six sigma. It is defined as:

$$\text{DPMO} = \frac{1,000,000 \times \text{number of defects}}{\text{Number of units} \times \text{number of opportunities per unit}}$$

Denominator: The number below the line in a ratio; divisor; population at risk.

Dependent variable: The event studied and expected to change whenever the independent variable is altered. Dependent variable is measured by the experimenter. Dependent variable is also known as a "response variable", "regressand", "measured variable", "responding variable", "explained variable", "outcome variable", "experimental variable", and "output variable". In graphs, dependent variable is positioned in y-axis (vertical).

Design-build: A project delivery system used in the construction industry. The design and construction services are contracted by a single entity known as the design-builder or design-build contractor, typically for an agreed lump-sum price.

Design failure: The manner in which a system, subsystem, or part fails to meet its intended purpose or function.

Design qualification (DQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems and processes have been designed in accordance with the requirements for good manufacturing practices (GMP). (WHO)

Design space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)

Detectability: The ability to discover or determine the existence, presence, or fact of a hazard. (ICH Q9)

Developing Countries Vaccine Manufacturers Network (DCVMN): Public health driven, international alliance of manufacturers, working to strengthen vaccine manufacturers through the provision of information and professional training programmes, technology improvements, innovative vaccine research and development, encouraging technology transfer initiatives, and educating the public about the availability of safe, effective and affordable vaccines for all people. DCVMN is established in the year 2000, sharing the vision of protecting all people against known and emerging infectious diseases, with the mission of increasing the quality and availability of vaccines affordable to all. Over the years the network grew reaching out today to include 44 vaccine



Developing Countries Vaccine
Manufacturers Network

manufacturers, in 16 countries and territories, producing and supplying over 40 different types of vaccines, in several presentations and using a variety of technology platforms totalling around 200 products. From those nearly 40 are prequalified by WHO. For details visit <http://www.dcvmn.org/>

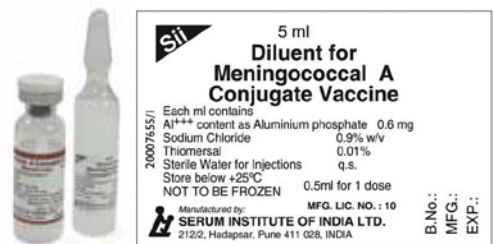
Deviation: Departure from an approved instruction or established standard (*USFDA*). For installation qualification: any discrepancy between the installation specifications and the actual (as found) installation. For operational qualification: any discrepancy between the protocol and the actual performed test, test function methodology, testing equipment, and testing material.

DFSS: See *DMADV*.

Diagnostic odds ratio: A measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a condition (disease) relative to the odds of the test being positive if the subject does not have the condition (disease). Also see *validity*.

$$\text{Diagnostic odds ratio} = \frac{\text{Positive likelihood ratio}}{\text{Negative likelihood ratio}}$$

Diluent: A liquid used to reconstitute lyophilized (freeze-dried) vaccines for administration. Diluents are not just for dissolving vaccines, they are designed to meet an individual vaccine's specific requirements in terms of volume, sterility, pH and chemical balance. Certain vaccine diluents include adjuvants and/or some antigens that are components of the final vaccine. For example, the diluent for Meningococcal A conjugate vaccine lyophilized (MenAfriVac) from Serum Institute of India Ltd., contains aluminium phosphate as adjuvant and thiomersal as preservative.



**MenAfriVac vaccine and its diluent
(Serum Institute of India Ltd.)**

Diluents are not interchangeable. Each lyophilized vaccine must be reconstituted with its own diluent that is provided together with the vaccine. Using the wrong diluent, substituting normal saline, or using sterile water makes the vaccine ineffective and less able to provide protection against disease. Fatal AEFI cases have been reported due to incorrect use of medications for reconstitution.

Direct access: Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domes-

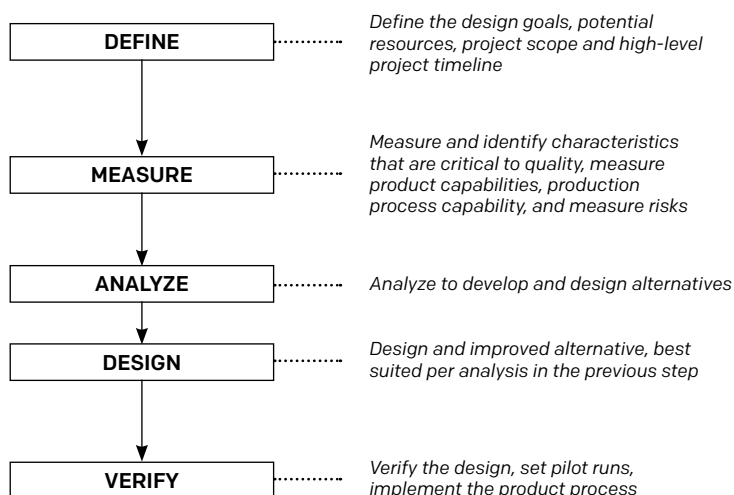
tic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information. (ICH E6/R1)

Dissipation: Result of an irreversible process taking place in inhomogeneous thermodynamic systems. Heat transfer is dissipative, because it is a transfer of internal energy from a high energy body to a low energy one.

Distributor: A receiving, warehousing and shipping site that delivers pharmaceutical products to pharmacies, hospitals, and healthcare centers. The distributor is an entity that buys noncompeting products or product lines, warehouses them, and resells them to retailers or direct to the end users or customers. There may be one or several distributors of pharmaceutical products between the manufacturer and the consumer. Sometimes the distributor is a commercial operation or company; at other times it could be a regional governmental or NGO facility. In any case, distributors receive relatively large shipments from manufacturers (or other distributors), warehouse them and sends smaller amounts of the product farther down the distribution chain. Distributors must ensure their facilities, procedures, and personnel do nothing to compromise the cold chain – and the quality of the product. (WHO)

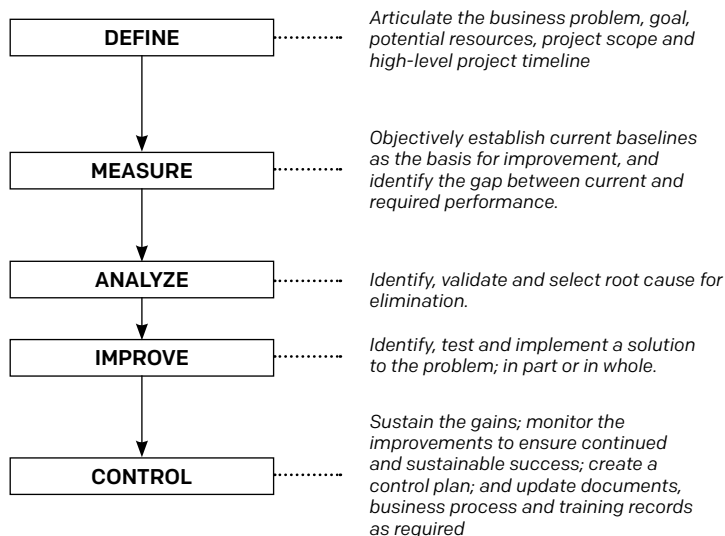
DMADV: (define, measure, analyze, design, and verify) - A project methodology, known as DFSS (design for six sigma), composed of five phases, mainly used for projects aiming at creating new product or process designs.

DMADV steps (Kartoglu)



DMAIC: (define, measure, analyze, improve and control) - A core tool used to drive six sigma projects and data-driven improvement cycle used for improving, optimizing and stabilizing business processes and designs. DMAIC is used for projects aiming to improve an existing process.

DMAIC steps (Kartoglu)



Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken. (ICH E6/Rev1)

Dosage form: The form of the FPP, e.g., tablet, capsule, elixir or suppository.



Tablet



Capsule

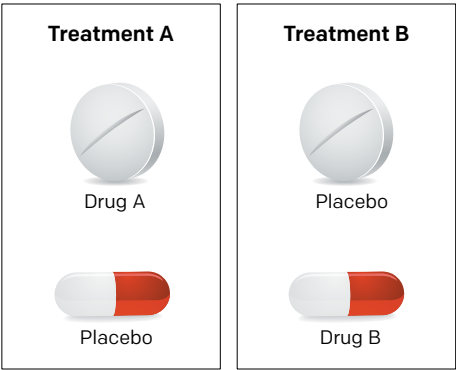


Suppository



Elixir

Various dosage forms



Double-dummy: A technique for retaining the blind when administering supplies in a clinical trial, when the two treatments cannot be made identical. Supplies are prepared for Treatment A (active and indistinguishable placebo) and for Treatment B (active and indistinguishable placebo). Subjects then take two sets of treatment; either A (active) and B (placebo), or A (placebo) and B (active). (*ICH E9*)

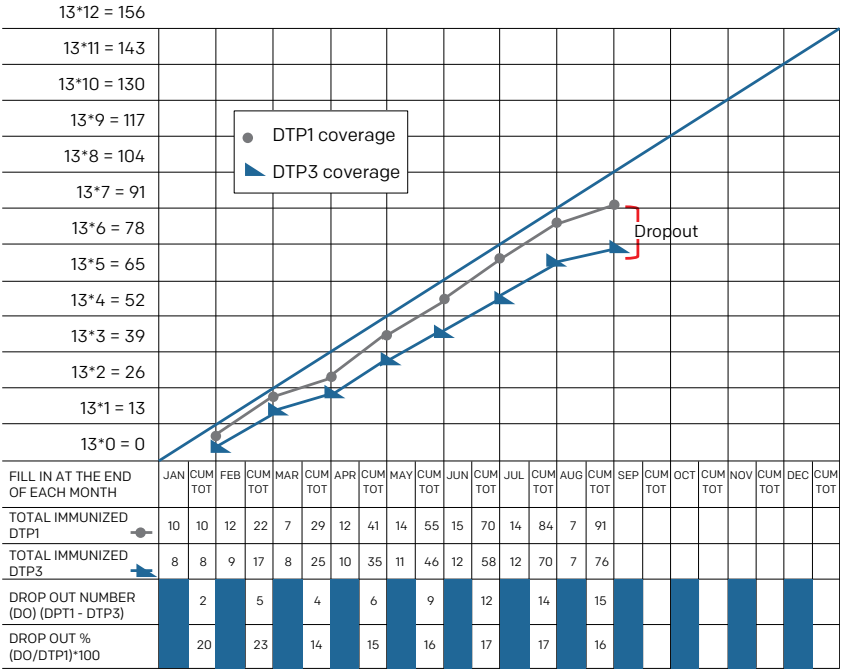
Double-dummy technique (Kartoglu)

Drill-down technique: A process of breaking the problem down into its component parts.

Dropout (clinical trial): A subject in a clinical trial who for any reason fails to continue in the trial until the last visit required of him/her by the study protocol. (*ICH E9*)

Dropout rate: The percentage of children failing to complete a particular vaccine course in a given time period. It is calculated for vaccines that requires more than one dose. (*WHO*)

Worked example of a monitoring chart for DTP1 and DTP3, WHO



$$\text{DTP1-DTP3 dropout rate} = \frac{\text{Doses of DTP1 administered} - \text{Doses of DTP3 administered}}{\text{Doses of DTP1 administered}} \times 100$$

Dropout rates can be easily monitored visually in Immunization Monitor charts. However, it should be noted that in immunization monitoring charts “cumulative” figures are used. In this sense, as for the time period, for example, dropout at the end of March takes into account of cumulating of dropouts in January, February and March. The dropout rate can be easily visually monitored in these charts as the gap between the line of DTP1 and of DTP3 cumulative vaccinations.

Drug product: The drug product is the finished dosage form of the product. The drug product contains the drug substance(s) formulated with other ingredients in the finished dosage form ready for marketing. Other ingredients, active or inactive, may include adjuvants, preservatives, stabilizers, and/or excipients. For vaccine formulation, the drug substance(s) may be diluted, adsorbed, mixed with adjuvants or additives, and/or lyophilized to become the drug product (*USFDA*). See *active pharmaceutical ingredient*.

Drug substance: The drug substance is the unformulated active (immunogenic) substance which may be subsequently formulated with excipients to produce the drug product. The drug substance may be whole bacterial cells, viruses, or parasites (live or killed); crude or purified antigens isolated from killed or living cells; crude or purified antigens secreted from living cells; recombinant or synthetic carbohydrate, protein or peptide antigens; polynucleotides (as in plasmid DNA vaccines); or conjugates. For combination vaccines, each active substance, which will be pooled, combined with other antigens and formulated, should be described. (*USFDA*)



Air cushions used as dunnage to void fill (Kartoglu)

Dunnage: Loose packing material used to protect TTSPs from damage during transport. (*WHO*)

E

Earliest expiry first out (EEFO): Material requirements are serviced in the order of items with the earlier date of consumption regardless of the date of entry or acquisition. FEFO (first expiry, first out) is also used with the same meaning, however, since it reminds FIFO (first in, first out), to prevent any confusion, EEFO is the preferred acronym. In vaccine vial monitor (VVM) based vaccine management systems, some vaccines with later expiry may be dispatched prior to earlier expiry vaccines if the VVM indicates that the vaccine may become unusable before the next dispatch period.

Electronic data integrator (EDI): A hybrid electronic instrument intelligently programmed like an electronic temperature indicator (ETI) with the report/data producing capabilities of an electronic data logging monitor (EDLM) that combines the features and functions of a go/no-go device (like an indicator) with the record retention and data tracking facility of an EDLM but with greater granularity and data management flexibility. It uses preprogrammed temperature threshold intelligence to integrate post-analytic functional steps that are typically performed by trained personnel. (WHO)



Q-tag® CLM doc from Berlinger & Co AG
PQS code E006/016



LogTag® TIC20 from
LogTag Recorders
PQS code E006/021



VaxAlert™ from Sensitech
PQS code E006/010

Examples of WHO PQS prequalified electronic data integrators

Electronic data logging monitor (EDLM): A small portable device that measures and stores temperature readings at predetermined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analyzed via proprietary hardware, software, desktop application or through hosted data-bases. (WHO)



Libero T11 from
Elpro-Buchs AG
PQS code E006/024



LogTag® TRIX-8 from
LogTag Recorders
PQS code E006/006

Examples of WHO PQS prequalified electronic data logging monitors

Electronic temperature indicator (ETI): A compact, portable device that measures, temperature over time by means of a built-in sensor. They come in a wide range of forms, features, configurations, cost and levels of performance. Their composition consists of four basic components: a thermistor sensor, a microprocessor, a memory chip, and a power source (lithium battery). (WHO)



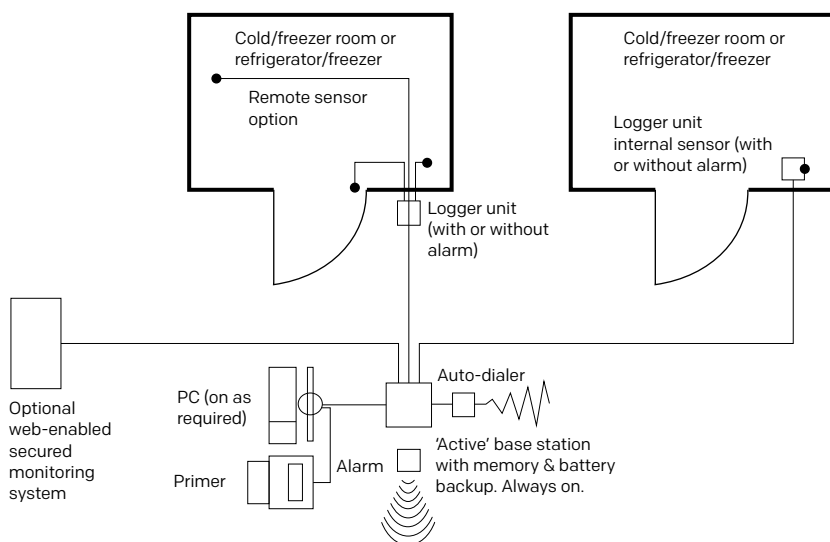
Vaxtag® from
LogTag Recorders
PQS code E006/013



Fridge-tag2® from
Berlinger & Co AG
PQS code E006/020

Examples of WHO PQS prequalified electronic temperature indicators

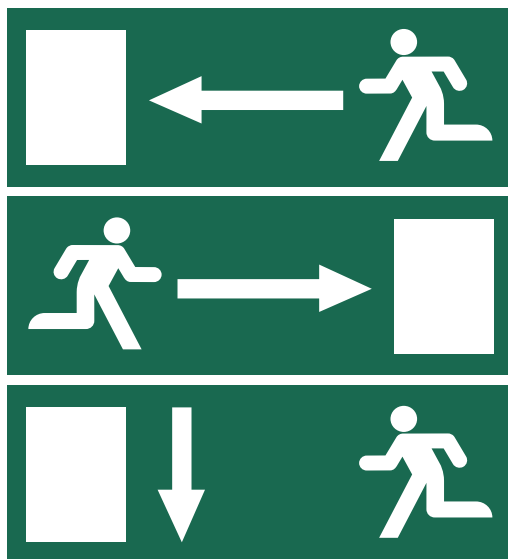
Electronic temperature monitoring and event logger system: System for recording and reporting air and/or product temperatures, with optional facilities for recording and reporting specific events such as door opening or defrost cycles, and for issuing alarms. Such systems may be user-programmable and may also be remotely monitored via a satellite link. (WHO)



Programmable electronic temperature monitoring and event logger system diagram (WHO)

Elimination (of disease): Reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts; continued intervention measures are required (WHO). Examples of elimination programmes currently sanctioned by the WHO include maternal and neonatal tetanus, measles, leprosy, onchocerciasis, trachoma and lymphatic filariasis. However, it should be noted that “reduction to zero of the incidence” may not be the case in some elimination programmes. For example, maternal and neonatal tetanus (MNT) elimination programme goal is to reduce MNT cases to such low levels that the disease is no longer a major public health problem. In this regard, the target incidence defined as “less than one case of neonatal tetanus per 1000 live births in all districts or equivalent administrative units of a country per year”.

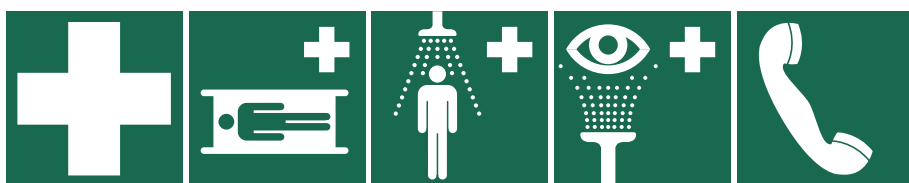
Emergency escape or first-aid signs: Signs giving information on emergency exits or first-aid or rescue facilities. They are always in green background color and could be either in rectangular or square shape.



Emergency exit / escape route



This way (supplementary information sign)



First-aid post

Stretcher

Safety shower

Eyewash

Emergency telephone
for first aid or escape**Examples of emergency escape or first-aid signs (EU)**

Endemic: The constant presence of a disease or infectious agent within a given geographic area or population group; may also refer to the usual prevalence of a given disease within such area or group. (*WHO*)

Environmental management system: A management system that allows for the identification of quality critical environmental aspects (such as temperature, humid-

ity, and/or other environmental factors) for the drug product and ensures that adequate processes to maintain that environment are in place. (*USP 1079*)

Epidemic: The occurrence in a community or region of cases of an illness (or an outbreak) with a frequency clearly in excess of normal expectancy. The number of cases indicating presence of an epidemic will vary according to the infectious agent, size and type of population exposed, previous experience or lack of exposure to the disease, and time and place of occurrence; epidemicity is thus relative to usual frequency of the disease in the same area, among the specified population, at the same season of the year. A single case of a communicable disease long absent from a population or the first invasion by a disease not previously recognized in that area requires immediate reporting and epidemiologic investigation; two cases of such a disease associated in time and place are sufficient evidence of transmission to be considered an epidemic. (*WHO*)

Epidemiology: The study of the distribution and determinants of health-related states and events in a population. (*WHO*)

EPP: Expanded polypropylene - Highly versatile closed-cell bead foam that provides a unique range of properties, including outstanding energy absorption, multiple impact resistance, thermal insulation, buoyancy, water and chemical resistance, ex-

ceptionally high strength to weight ratio and 100% recyclability. EPP can be made in a wide range of densities, from 15 to 200 grams per litre, which are transformed by moulding into densities ranging from 18 to 260 grams per litre. Individual beads are fused into final product form by the steam-chest moulding process resulting in a strong and lightweight shape. Porous EPP is comprised of cylinder-shaped polypropylene beads, which adds air space between the beads in the final moulded form, which enhances beneficial acoustical insulating effects and re-

duces weight. EPP resistance to heat flow (R-value) is around 3.5 for every 3 cm thickness of material. EPP boxes are cleanable, reusable and recyclable.

EPS: Expanded polystyrene - EPS is rigid, closed cell, thermoplastic foam material. EPS is produced from solid beads of polystyrene. Expansion is achieved by virtue of small amounts of gas contained within the polystyrene bead. The gas expands when



Porous expandable polypropylene beads (DS Smith Plastics and Foam Products)

heat in the form of steam is applied, thus forming closed cells of EPS. These cells occupy approximately 40 times the volume of the original polystyrene bead. The large EPS blocks beads can be fabricated per specification to form customised shapes. EPS is made of 98% air, making it one of the lightest packaging materials. EPS resistance to heat flow (R-value) is around 4 for every 3 cm thickness of material. EPS boxes are cleanable, reusable and recyclable. EPS is non-toxic and chemically inert (fungi and bacteria cannot live on it).



Expandable polystyrene beads
(XXL Photo, Shutterstock)



Block moulded EPS boxes
(Kartoglu)

Equivalence trial: A trial having the primary objective of showing that the response to two or more treatments differs by an amount that is clinically unimportant. Showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences usually demonstrates this. (WHO)

Eradication (of disease): Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed (WHO). In 1979, a global commission certified that smallpox had been eradicated, and this certification was officially accepted by the 33rd World Health Assembly in 1980.

Currently, dracunculiasis and polio are the two eradication programmes sanctioned by the WHO.



**The official 1979 declaration that
"smallpox has been eradicated
from the world" (WHO)**

Essential documents (clinical trials): Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated:

- before the clinical phase of the trial commences,
- during the clinical conduct of the trial, and
- after completion or termination of the trial.

A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both (*WHO and ICH E6/R1*).

Essential documents as listed by the ICH E6/R1 by title, purpose and location in files (marked with grey shading)

Title of document	Purpose	Location in files of	
		Investigator/Institution	Sponsor
Before the clinical phase of the trial commences			
Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator		
Signed protocol and amendments, if any, and sample case report (CRF) form	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF		
Inform consent form (including all applicable translations)	To document the informed consent		
Any other written information given to trial subject	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent		

Title of document	Purpose	Location in files of	
		Investigator/Institution	Sponsor
Advertisement for subject recruitment (is used)	To document that recruitment measures are appropriate and not coercive		
Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial		
Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available		
Signed agreement between investigator/institution and sponsor	To document agreements		
Signed agreement between investigator/institution and CRO	To document agreements		Where required
Signed agreement between sponsor and CRO	To document agreements		
Signed agreement between investigator/institution and authority(ies) (where required)	To document agreements		
Dated, documented approval/favourable opinion of IEC of the following: <ul style="list-style-type: none"> ■ protocol and any amendments ■ CRF (if applicable) ■ informed consent form(s) ■ any other written information to be provided to the subject(s) ■ advertisement for subject recruitment (if used) ■ subject compensation (if any) ■ any other documents given approval/ favourable opinion 	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)		
Institutional Review Board/Independent Ethics Committee composition	To document that the IRB/IEC is constituted in agreement with GCP		Where required
Regulatory authority(ies) authorization/approval notification of protocol (where required)	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	Where required	Where required

Title of document	Purpose	Location in files of	
		Investigator/Institution	Sponsor
Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects		
Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests		
Medical/laboratory/technical procedures/tests: <ul style="list-style-type: none"> ■ certification or ■ accreditation or ■ established quality control and/or external quality assessment or ■ other validation (where required) 	To document competence of facility to perform required test(s), and support reliability of results	Where required	
Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		
Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials		
Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability		
Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational product(s) to be used in the trial		
Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment		Third party if applicable

Title of document	Purpose	Location in files of	
		Investigator/Institution	Sponsor
Master randomization list	To document method for randomisation of trial population		
Pre-trial monitoring report	To document that the site is suitable for the trial (may be combined with "trial initiation monitoring report")		
Trial initiation report	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with "Pre-trial monitoring report")		
During the clinical phase of the trial commences			
Investigator's Brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available		
Any revision to: Protocol amendment(s) and CRF ■ Informed consent form ■ Any other written information provided to subjects ■ Advertisement for subject recruitment (if used) any other documents given approval/ favourable opinion	To document revisions of these trial related documents that take effect during trial		
Dated, documented approval/favourable opinion of Institutional Review Board/Independent Ethics Committee of the following: protocol amendment(s) ■ revision(s) of: ■ informed consent form <ul style="list-style-type: none"> any other written information to be provided to the subject advertisement for subject recruitment (if used) any other documents given approval/favourable opinion ■ continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).		

Title of document	Purpose	Location in files of	
		Investigator/Institution	Sponsor
Regulatory authority(ies) authorizations/approvals/notifications where required for protocol amendment(s) and other documents.	To document compliance with applicable regulatory requirements	Where required	
Curriculum vitae for new investigator(s) and/or sub-investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects		
Updates to normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and ranges that are revised during the trial		
Updates of medical/laboratory/technical procedures/tests: certification or ■ accreditation or ■ established quality control and/or external quality assessment or ■ other validation (where required)	To document that tests remain adequate throughout the trial period	Where required	
Documentation of investigational product(s) and trial-related materials shipment	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability		
Certificate(s) of analysis for new batches of investigational product(s)	To document identity, purity, and strength of investigational product(s) to be used in the trial		
Monitoring visit reports	To document site visits by, and findings of, the monitor		
Relevant communications other than site visits, such as letters, meeting notes and notes of telephone calls.	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting		
Signed informed consent forms	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject		

Title of document	Purpose	Location in files of	
		Investigator/Institution	Sponsor
Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject		
Signed, dated and completed case report forms (CRF)	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	Copy	Original
Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded	Copy	Original
Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with safety reporting		
Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s)/IEC (s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with adverse drug reaction reporting and safety reporting	Where required	
Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information in accordance with reporting of safety information		
Interim or annual reports to IRB/IEC and authority(ies)	Interim or annual reports provided to IRB/IEC in accordance with progress report requirements and to authority(ies) in accordance with adverse drug reaction reporting		Where required
Subject screening log	To document identification of subjects who entered pre-trial screening		Where required
Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject		

Title of document	Purpose	Location in files of	
		Investigator/Institution	Sponsor
Subject enrolment log	To document chronological enrolment of subjects by trial number		
Investigational product(s) accountability at the site	To document that investigational product(s) have been used according to the protocol		
Signature sheet	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs		
Record of retained body fluid/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated		
After completion or termination of the trial			
Investigational product(s) accountability at the site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor		
Documentation of investigational product(s) destruction	To document destruction of unused investigational products by sponsor or at site	If destroyed at site	
Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time		
Audit certificate (if available)	To document that audit was performed		
Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		
Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred		
Final report by investigator to IRB/IEC where required, and where applicable, to the regulatory authority(ies)	To document completion of the trial		
Clinical study report	To document results and interpretation of trial	If applicable	

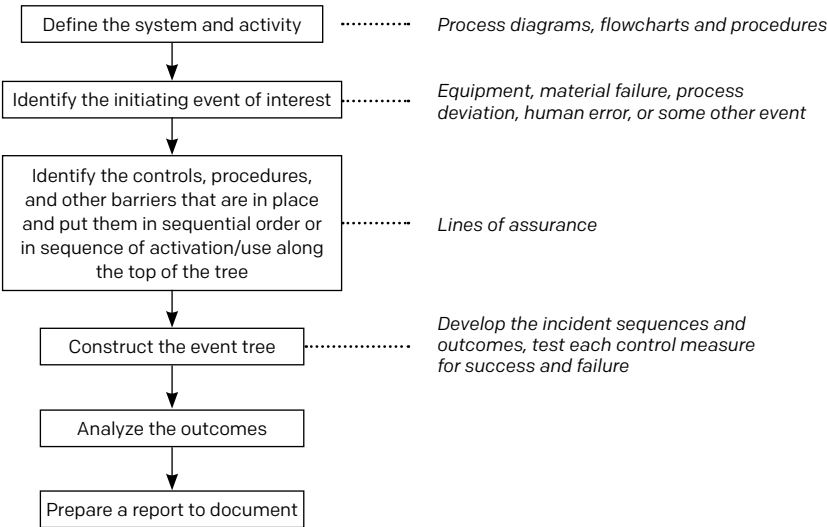
EUR pallet: The standard European pallet as specified by the European Pallet Association (EPAL). The EUR pallet is 1200x800x144 mm; it is a four way pallet made of wood that is nailed with 78 special nails in a prescribed pattern.



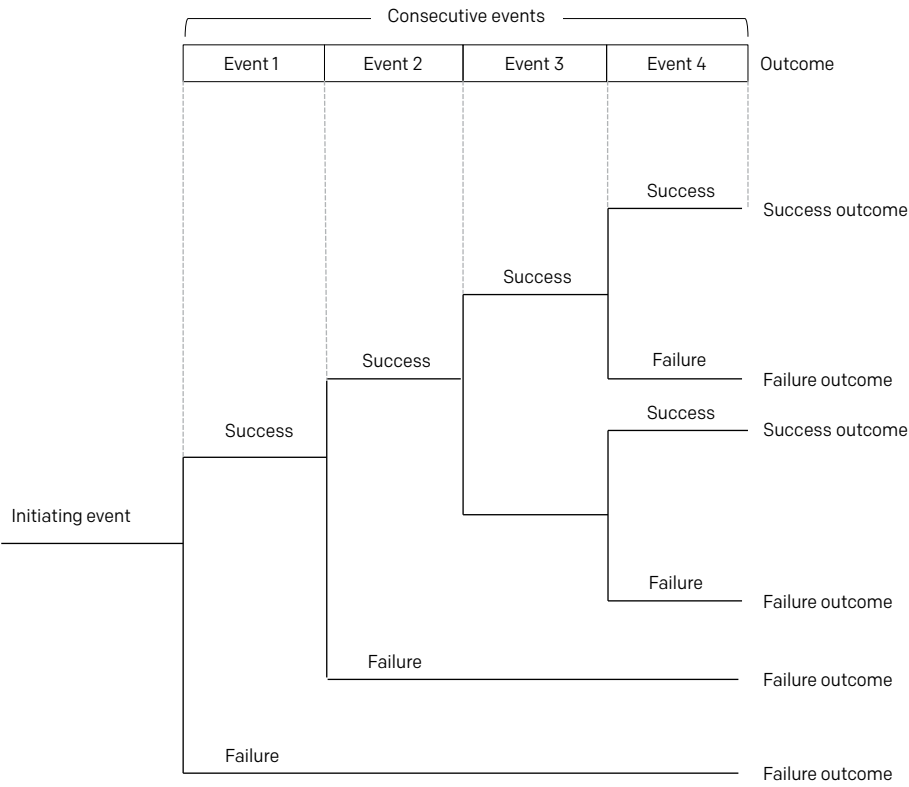
EUR pallet in use (Andrea Crisante, Shutterstock)

Event tree analysis (ETA): A qualitative (and potentially quantitative), graphical, structured, inductive tool used to examine the range of impacts that an incident could have within a system should the designed controls within that system work or not work as intended. It is a modified form of a “decision tree”. The initiating event of interest is the event that triggers all of the sequential events. By nature, it could be an equipment or material failure, process deviation, human error, or some other event. Following this, “lines of assurances”, the controls, procedures and other barriers that are already in place should be listed on top of the tree in a sequential order of activation. Each of these controls then must be evaluated both for success (upward line in the tree) and failure (downward line in the tree) Once all the sequences are completed, the outcomes should be described and named. In the case of available data, probabilities can be calculated.

Event tree analysis process (Kartoglu)



A typical event-tree diagram(Kartoglu)



Excipient: A substance or compound, other than the API and packaging materials, that is intended or designated to be used in the manufacture of a FPP. (WHO)

Expected monetary value (EMV): A calculated value based on the probability and the cost of outcome to make comparisons between a range of uncertain outcomes. EMV is frequently used in comparing the control strategies (in monetary terms) established in response to risk assessment.

$$EMV = [Likelihood\ of\ occurrence] \times [cost\ of\ outcome]$$

Expedited review: Expedited review procedure is directed at countries that source their vaccines either through UN agencies or by importing directly from manufacturers using the WHO prequalified list of products, and that wish to ensure that these products are under appropriate regulatory oversight, but may lack the resources to

carry out a regulatory approval procedure. Because in executing the prequalification process WHO assures that the necessary regulatory functions are in place, countries that source their vaccines using the WHO prequalified list could expedite the regulatory process for these products by using a fast-track procedure. Such a procedure would recognize the contribution of the WHO prequalification process, while facilitating development of national regulatory capacity. (It is essential, however, to remember the responsibility of all importing countries to develop and implement a system for the detection and resolution of AEFIs). The aim of the expedited procedure is two-fold: a) to propose a methodology that will be in accord with national regulations⁴ and international standards of regulatory approval of products; b) to continue to provide timely access to vaccines used in national immunization programmes that meet standards of assured quality. In addition, it can help NRAs define priorities, including placing more emphasis on adverse event surveillance - the most relevant function for all countries receiving prequalified vaccines from any source. (WHO)

Experimental study: A study in which the conditions are under the direct control of the investigator. Such studies may include random allocation of subjects to treatment or control groups and blinding of subject and investigator to the placement status (i.e., whether in the treatment or control group). (WHO)

Expert Committee for Biological Standardization (ECBS): The WHO Expert Committee on Biological Standardization is commissioned by WHO to establish detailed recommendations and guidelines for the manufacturing, licensing, and control of blood products, cell regulators, vaccines and related in vitro diagnostic tests. Members of the Expert Committee are scientists from national control agencies, academia, research institutes, public health bodies and the pharmaceutical industry acting as individual experts and not as representatives of their respective organizations or employers. The decisions and recommendations of the Committee are based entirely on scientific principles and considerations of public health.

The Expert Committee on Biological Standardization meets on an annual basis since 1947 and is responsible for the establishment of the WHO International Biological Reference Preparations and for the adoption of the WHO Recommendations and Guidelines. Meeting reports and recommendations are published known as the WHO Technical Report Series (TRS). The Expert Committee directly reports to the Executive Board, which is the executive arm of the World Health Assembly. (WHO)

Expert Committee on Specifications for Pharmaceutical Preparations (ECSP):

The WHO Expert Committee on Specifications for Pharmaceutical Preparations is commissioned by WHO to develop independent and practical norms and standards, and guidelines for the quality assurance of medicines. Standards are developed by the Committee through worldwide consultation and an international consensus building process. Meeting reports and recommendations are published known as the

WHO Technical Report Series (TRS). ECSPP meets on an annual basis since 1948, and reports directly to the Executive Board of the World Health Assembly. (WHO)



Expiry date on a secondary package of a drug product (Kartoglu)

Expiry date: The date given on the individual container (usually on the label) of a final product up to and including which, the product is expected to remain within specifications, if stored as recommended. It is established for each batch by adding the shelf-life period to the date of manufacture or the starting date of the last potency test.

If the expiry date includes month and the year, recommended display is as two digit month and four digit year, e.g., 09.2016. In this format, the last day of the month is assumed. If the expiry date includes the day as well, it is recommended two-digit day, two-digit month and four-digit year, e.g., 04.07.2017.

Exposure: Having contact with an infectious agent in a way that experience has shown may cause disease. (WHO)

External distribution: Transport of TTSPs through various steps in the customer's supply chain (i.e., transport from a pharmaceutical manufacturer's distribution centre, to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient). Contrast with *internal distribution*. (WHO)

F

Facility management: The professional management of building infrastructure. Responsibilities of the facility manager include day-to-day operation, space allocation and management of changes to the building, management of health and safety, fire safety, security, maintenance, testing and inspection, cleaning, contingency/disaster planning and tendering for outsourced contracts relating to any of these activities. (*WHO*)

Failure: The loss of a function under stated conditions.

Failure cause: Defects in requirements, design, process, quality control, handling or part application, which are the underlying cause or sequence of causes that initiate a mechanism leading to a failure mode over a certain time. Failure cause also tells us “how” the “failure mode” has occurred.

Failure effect: Consequences of a failure on operation, function or status of an item. Failure effects may appear immediately as well as in time. If the failure effect applies to the item under analysis, it is called “local effect”. “Next higher level effect” is the failure effect that applies at the next higher indenture level. It is called “end effect” when the failure effect is at the highest indenture level or total system.

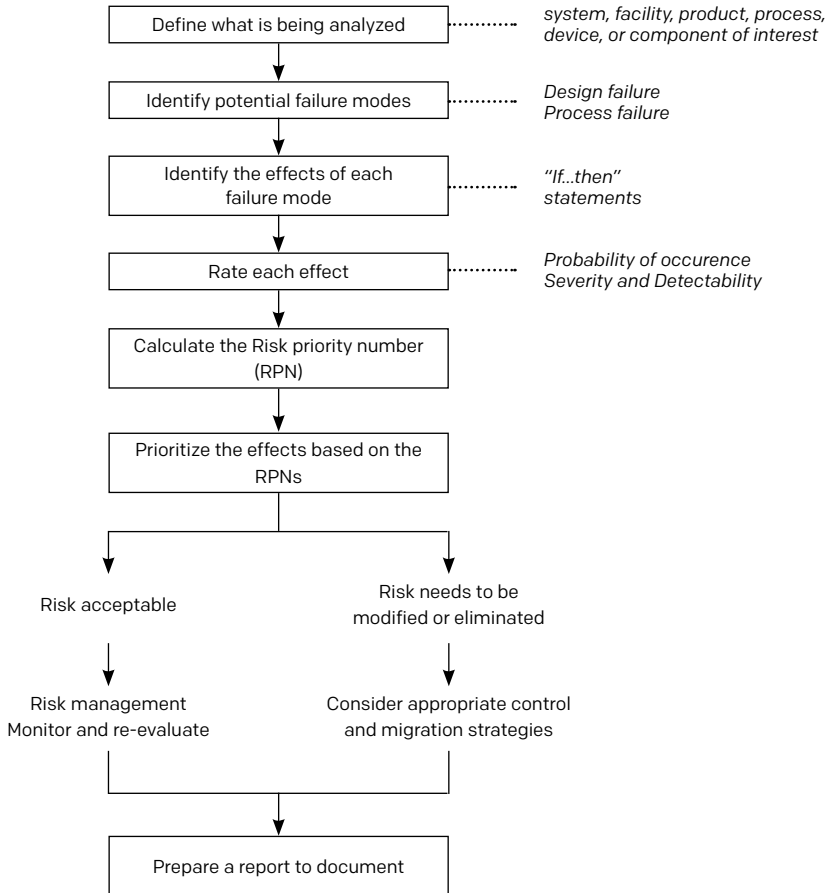
Failure mode: The specific way by which a failure occurs in terms of failure of the item function under investigation. It clearly describes an end failure state of the item or function/process in case of a system under consideration. Failure mode also tells us “what” has failed.

Failure mode and effects analysis (FMEA): A qualitative (semi-quantitative or quantitative), structured, inductive risk assessment tool used to identify known and potential failure modes of facilities, systems, products, equipment, or components, as well as to identify the failure’s impact. Failure mode, effects, and criticality analysis (FMECA) is a slightly expanded version of the FMEA with the main difference in the calculation of the “risk priority number”.

A typical FMEA worksheet									
Process step	Potential failure mode	Potential failure effect	Severity of consequence (S)	Potential causes	Likelihood of occurrence (L)	Current process controls	Detectability (D)	Risk priority number	Actions recommended
What is the step?	In what ways can the step go wrong?	What is the impact?	How severe is the effect? (risk scale)	What causes the step to go wrong?	How frequently is the cause likely to occur?	What are the existing controls that either prevent the failure mode from occurring or detect it should it occur?	How probable is detection of the failure mode or its cause?	(Calculated) S x L x D	What are the measures for reducing the occurrence of the cause for improving its detection, likelihood of occurrence and reduce the severity impact?

Once potential failure modes and effects of each failure mode are fully listed, probability of occurrence, severity and detectability of each effect need to be scored. Multiplication of these factors gives the “risk priority number” or “risk index”. Risks need to be evaluated whether they are acceptable or not. In the case of risk being acceptable, it should be monitored and re-evaluated as part of risk management. If risk need to be modified and/or eliminated, appropriate control and mitigation measures need to be considered.

FMEA/FMECA process (Kartoglu)



Failure mode, effects, and criticality analysis (FMECA): Extended version of the FMEA. See *failure mode and effects analysis*.

False discovery rate: Proportion of false positives from a diagnostic test to number of negative conditions (disease) by golden test. Also see *validity*.

False negative rate: Proportion of false negatives from a diagnostic test to number of positive conditions (disease) by golden test. Also see *validity*.

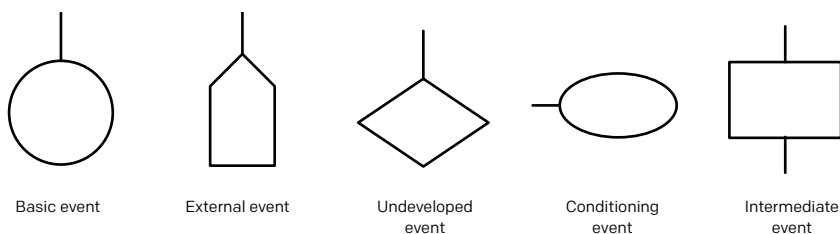
False omission rate: Proportion of false negatives which are incorrectly rejected (diagnosed with a negative test outcome). Also see *validity*.

Fault tree analysis (FTA): A qualitative (and potentially quantitative), graphical, structured, deductive tool used to define a particular event and identify its causes. FTA uses the Boolean logic to combine a series of lower-level events. FTA is most appropriate when trying to identify the potential root cause(s) of a real or hypothetical event. These root causes are called “basic events” in an FTA. The defined problem (unwanted event) for the FTA is the “top event”.

In constructing the fault tree diagram, the “primary event” symbols are typically used as follows:

- **Basic event** - failure or error in a system component or element (example: switch stuck in open position)
- **External event** - normally expected to occur (not of itself a fault)
- **Undeveloped event** - an event about which insufficient information is available, or which is of no consequence
- **Conditioning event** - conditions that restrict or affect logic gates (example: mode of operation in effect)

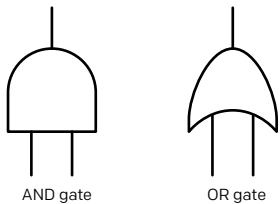
Event symbols used in FTA diagram



“Gate symbols” describe the relationships between input and output events. They are derived from Boolean logic symbols and typically used as follows:

- **OR gate** - the output occurs if any input occurs (that the individual events below the OR gate are necessary and also sufficient to cause the preceding event)
- **AND gate** - the output occurs only if all inputs occur (that the individual events below the AND gate are necessary but not sufficient on their own to cause the preceding event)

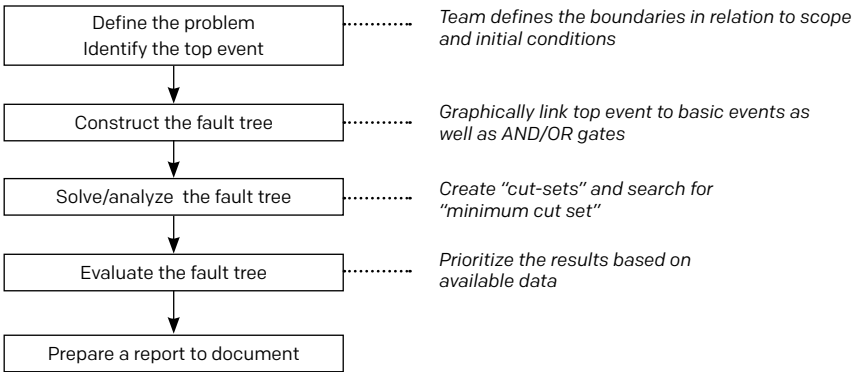
Major gate symbols used in FTA



In advanced versions of fault tree diagrams more sophisticated OR and AND gates are used, such as “exclusive OR gate” which the output occurs if exactly one input occurs, “priority AND gate” which the output occurs if the inputs occur in a specific sequence specified by a conditioning event and “inhibit gate” which the output occurs if the input occurs under an enabling condition specified by a conditioning event. Again, in more advanced and complex fault tree analysis, related fault tree diagrams may be connected to each other through “transfer symbols”.

Once the diagram is completed, it must be “solved”. In this stage, “cut sets” are created; cut sets are all of the combinations of events that can cause the top event to occur. In addition to this, “minimum cut set” need to be found that is the minimum number of events required for the top event to occur.

Fault tree analysis process (Kartoglu)



Feedback report: A report that (a) informs lower levels about their performance and in some cases providing additional information about reporting from other facilities; and (b) informs managers at higher levels about how the system is functioning. (WHO)

Sample quarterly feedback report for immunization services (WHO)

Date covered from:

To:

Facility name	Reports sent on time	Commodity name	Open- ing bal- ance (doses)	Re- ceived (doses)	Used (dos- es)	Loss- es/ adjust- ments (doses)	End bal- ance (doses)	AMC (doses)	Stock level (months)	Remarks
A	B	C	D	E	F	G	H	I	J	K
		OPV								
		DTP+HepB								
		BCG								
		BGC diluent								
		Measles								
		Measles diluent								
		Reconstitution syringe								
		AD syringe BCG								
		AD syringe (0.5 ml)								
		Safety box								
		OPV								
		DTP+HepB								
		BCG								
		BGC diluent								
		Measles								
		Measles diluent								
		Reconstitution syringe								
		AD syringe BCG								
		AD syringe (0.5 ml)								
		Safety box								

All stock management systems should be designed with feedback mechanisms. Feedback should be given not only when there is a problem; positive feedback is extremely important for the lower levels. Facilities also would like to see in feedback reports how their performance would fit within the overall system.

Feedback reports inform lower levels about their performance and provide information about other facilities in the same level. They may point errors in incoming reports and provide guidance on how to correct them. In addition, feedback reports let the person sending the report knowing his/her work has been received and processed. Feedback reports may be used to motivate lower levels to send complete, error-free reports on time by reporting which sites are producing quality reports.

Finished pharmaceutical product (FPP): A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs.

Firefighting signs: A permanent sign giving information on the location of firefighting equipment. They are always in red background color and could be either in rectangular or square shape.



Fire hose



Ladder



Fire extinguisher



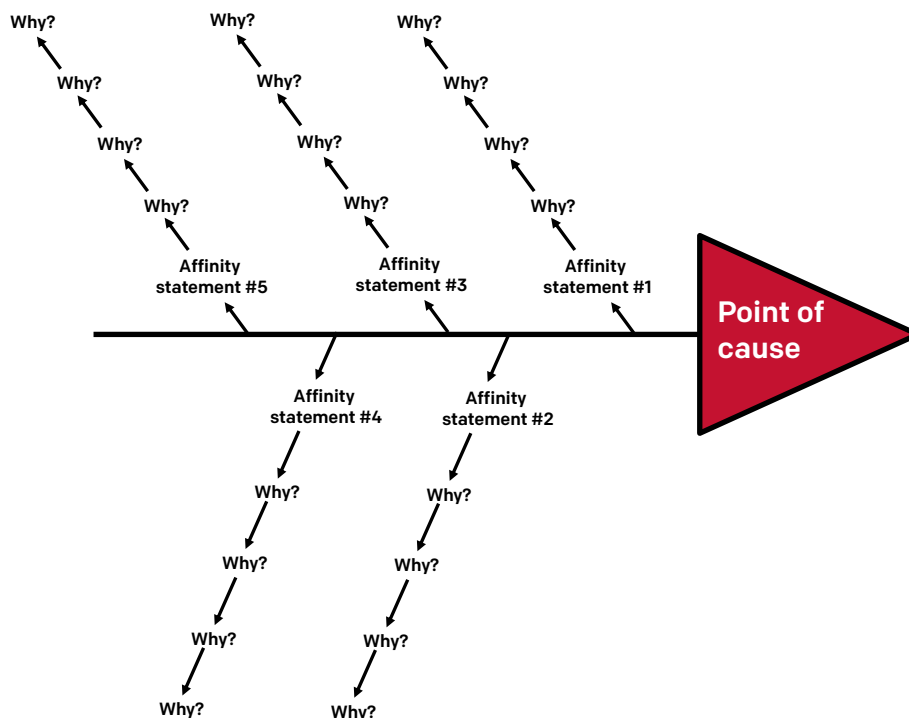
Emergency fire telephone

Examples of firefighting signs (EU)

First in first out (FIFO): Material requirements are serviced in order of items with the date of entry or acquisition. FIFO does not take into account the expiry date of the product; it assumes the expiry date of a latest arrival of a product will have longer expiry date compared to earlier arrival of the same product - which is not the case always. Because of this reason, with the increasingly complex supply provisions, EEFO (earliest expiry, first out) is now the preferred way to manage stocks.

Fishbone diagram: Causal diagram showing the causes of a specific event. It is also referred as Ishikawa diagram after its creator. It is frequently used in product design as well as quality defect prevention. Some refer to the fishbone diagrams as the 5 whys diagram since it illustrates the thought process behind the 5 whys analysis. It shows the Point of Cause in the "head" of the fishbone, the affinity statements as the first why of each "rib" or "leg," and a drill down of "why" phrases (preferably 5) for

Fish bone diagram (Kartoglu)



each affinity statement. Causes are usually grouped into major categories to identify these sources of variation. The categories typically include methods, people, machines, materials, measurements and environment. These categories vary from sector to sector: Manufacturing industry typically uses 5Ms (machine, method, material, manpower and measurement).

Flooded battery: A type of battery used to power solar refrigerators. Flooded batteries contain liquid sulphuric acid electrolyte that is potentially dangerous and requires corrective maintenance. (WHO)

Forecasting: A management function that estimates the quantities of products a programme will dispense to users for a specific period of time in the future.

Freeze indicator: Go/no-go type indicator providing a signal only when exposed to temperatures lower than a predetermined threshold temperature. They could be chemical or electronic. Electronic ones have better accuracy compared to its chem-



Examples of electronic freeze indicators

ical versions. Threshold temperature for freeze indicators are usually set as to 0°C while WHO prequalified models have -0.5°C as threshold to cover all alarms under the 0°C (with +/-0.5°C accuracy). See *threshold indicator*.

Freeze-thaw (cycle) studies: A series of low and high temperature exposures of the product to analyze the impact of freezing on its physical structure and chemical components. In a typical freeze-thaw study, the product is exposed to -20°C to -30°C for freezing (usually below its known freezing point) and to room temperature for thawing in repeated cycles (usually up to five). For example, D antigen quantitation is studied for IPV during freeze-thaw studies.

Freezer room: A purpose made insulated enclosure fitted with refrigeration equipment which maintains a set temperature below 0°C. (*WHO*)

Frozen control: “Control” is a subject closely resembling the factor under study and thereby serving as a comparison/reference sample when test results are evaluated. In shake test, the control vial is always a purposely frozen vial, which constitutes a negative control. As reference, the frozen control sample will sediment faster than non-frozen samples. See also *shake test*.

Full quality assurance: A few products (e.g., cold rooms, solar power systems and event logger type temperature monitoring systems) require quality assured on-site installation and commissioning if they are to operate successfully. An additional type of verification protocol known as a Quality Assurance (QA) protocol applies to such equipment. A QA protocol is installation-specific and is intended to form part of the contractual agreement with the equipment supplier/installer. (*WHO*)



g-force: (gravitational force) A measurement of the type of acceleration that indirectly causes weight. When the g-force acceleration is produced by the surface of one object being pushed by the surface of another object, the reaction-force to this push produces an equal and opposite weight for every unit of an object's mass. See *damage indicator*.



GAVI: Created in 2000, GAVI is an international organization - a global Vaccine Alliance, based in Geneva, Switzerland, bringing together public and private sectors with the shared goal of creating equal access to new and underused vaccines for children living in the world's poorest countries. For

more information see <http://www.gavi.org/>

Generic products: The term generic product has somewhat different meanings in different jurisdictions. Use of this term is therefore avoided as much as possible, and the term multisource pharmaceutical product is used instead. Generic products may be marketed either under the approved non-proprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different from those of the innovator products. Where the term generic product is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs. (WHO)

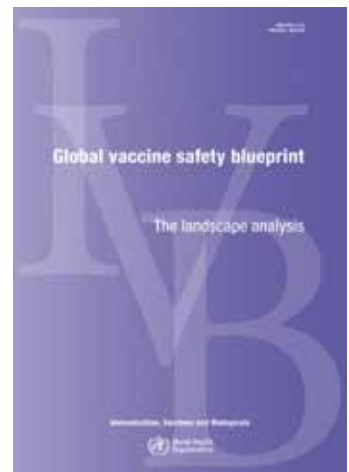
Global Advisory Committee on Vaccine Safety (GACVS): A global standing advisory committee that provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short or long term national immunization programmes. This includes providing advice on urgent matters as needed. Issues to be considered by the Committee are jointly decided by the WHO Secretariat and the Committee. GACVS has 14 members, who serve in their personal capacity and represent a broad range of disciplines covering immunization activities. GACVS members are acknowledged experts from around the world selected from, but not necessarily restricted to, disciplines such as epidemiology, statistics, paediatrics, internal medicine, pharmacology and toxicology, infectious diseases, public health, immunology and autoimmunity, vaccinology, pathology, ethics, neurology, drug regulation and vaccine safety. (WHO)

Global Vaccine Safety Blueprint: A document published by the WHO to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods. The blueprint strategic goals include:

- To assist low and middle income countries (LMIC) to have at least minimal capacity for vaccine safety activities.
- To enhance capacity for vaccine safety assessment in countries that introduce newly-developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines.
- To establish a global vaccine safety support structure.

The Global Vaccine Safety Blueprint is not the first document to draw attention to the need for improved global “vaccine pharmacovigilance.” Several organizations and partners, including WHO, UNICEF, GAVI and many international technical agencies, are involved in various aspects of vaccine pharmacovigilance either directly or indirectly. As a set of global strategies, however, the Global Vaccine Safety Blueprint represents an attempt to leverage international commitment and to set out a framework for coordinated action that will raise the level and accuracy of vaccine safety monitoring globally, and will enable cases of AEFI to be investigated wherever they occur.

A substantial proportion of AEFI results from inadequate handling and administration. Strategies to ensure



Two major documents for the global vaccine safety (WHO)

safe programmatic usage of vaccines are devised by immunization programmes. They are not addressed in this document that focuses on the effects related, or believed to be related, to the vaccine product themselves. Separate guidance documents are available to address vaccine management and immunization techniques, in particular from WHO. For details see <http://goo.gl/wbl2Zy> and <http://goo.gl/zaLkNR>

Global Vaccine Safety Initiative (GVSI): WHO initiative launched in 2012, set up to implement the “Global Vaccine Safety Blueprint” strategy. The initiative comprises a framework of eight strategic objectives aimed at enhancing global vaccine safety activities. The strategic objectives focus on building and supporting a systemic approach to vaccine pharmacovigilance in all low and middle-income countries. The eight strategic objectives are:

1. Strengthening vaccine safety monitoring in all countries.
2. Strengthening the ability of countries to evaluate vaccine safety signals.
3. Developing vaccine safety communication plans at country level to ensure awareness of vaccine risks and benefits, understand perceptions of risk, and prepare for managing any AEFI and crises promptly.
4. Developing internationally harmonized tools and methods for vaccine pharmacovigilance.
5. Advocating for the establishment of a legal, regulatory and administrative framework to ensure compliance with vaccine pharmacovigilance requirements at national, regional and international levels.
6. Facilitating the strengthening of regional and global technical support platforms for a vaccine pharmacovigilance system that meets countries’ expressed needs.
7. Making advice on vaccine safety issues available to support vaccine safety systems at national, regional and international levels.
8. Facilitating the development of systems for appropriate interaction between national governments, multilateral agencies, and manufacturers at national, regional and international levels.

The GVSI is neither a legal entity, nor a partnership. It is a WHO mechanism for enhancing vaccine safety by providing a framework for WHO to convene its member states and partners for the implementation of the Global Vaccine Safety Blueprint. As a forum for collaboration between vaccine safety stakeholders, it highlights existing tools and resources, creates synergies, and prevents duplication of efforts and wasted resources towards the achievement of its mission. The work of the GVSI is supported by the WHO GVSI Secretariat.

Also see *Global Vaccine Safety Blueprint*.

Globally Harmonized System of Classification and Labelling of Chemicals

(GHS): An international agreed-upon system created by the United Nations, designed to harmonize and regulate classification and labelling standards of hazardous materials. GSH was created at the 1992 Rio Conference on Environment and Development.

Gold standard: A diagnostic test or benchmark that is the best available and current preferred method of diagnosing a particular condition (disease). All other methods available and new tests developed to diagnose the same condition should be validated against the gold standard. For example, “phase control microscopy” was used as a “golden test” for validating the “shake test” in diagnosing the freeze damaged aluminium adjuvanted vaccines. Also see *validity*.

Good clinical practice (GCP): An international ethical and scientific quality standard that is provided by ICH (E6/R1) for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. The guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects. ICH lists 13 principles for GCP:

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented. For full text see <http://goo.gl/iTOW3a>

Good laboratory practice (GLP): A quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. GLP principles may be considered as a set of criteria to be satisfied as a basis for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions and the traceability of data. (*PDA*)

Good regulatory practice (GRP): GRP aims to improve the efficiency and effectiveness of regulatory agencies and of regulators themselves (*WHO*). The elements of GRP for a regulatory agency may comprise, but are not limited to:

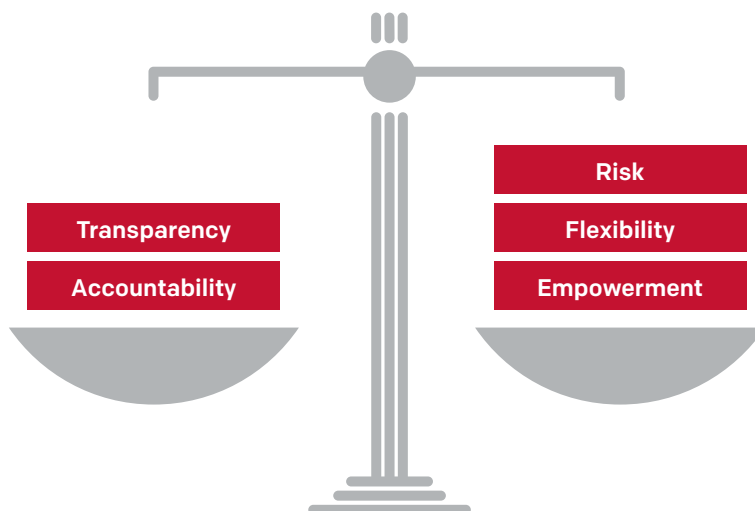
- Definition of the organization's mission, vision and functions;
- Mechanisms to ensure that the organization is accountable to government, those regulated, and the public;
- Possibility to assess attainment of objectives;
- Mechanisms to ensure that outcomes are transparent to applicants, health professionals, and public;
- Commitment to equity;
- Arguments used to reach decision accessible to the public;
- Reasonable duration of assessment without compromising quality, safety & efficacy;
- Expedite review for orphan and outstanding public health- value medicines;
- Provisions for appeals and complaints;
- Ensuring that staff are:
 - suitably qualified; and
 - have the necessary facilities to perform their work at a high standard; and

- are appointed by a fair and transparent mechanism; and
- are of high integrity.
- Existence of a human resource development programme;
- Mechanisms for appeal and for citizens' complaints;
- Access to appropriate knowledge and technology;
- Citizens are provided with accurate and appropriate medicines information;
- Mechanisms to ensure quality of operating procedures.

The elements of GRP are inter-related and often overlap.

Modern management strategies involve giving more flexibility and responsibility to managers and staff at each level, and the ability to manage risk. This extra responsibility is sometimes referred to as empowerment. Consequently, in order to balance the extra power, there must be greater transparency and accountability.

The regulatory balance (WHO)



Gross storage capacity: The gross free volume of a load support system available for storing SKUs. This volume is measured between the shelves of a shelving unit, or between the support beams of a racking system. (WHO)

Grossing factor: The actual internal volume of a cold room/freezer room, refrigerator or freezer, divided by the net volume of product that it can accommodate. (WHO)



Harm: Damage to health, including the damage that can occur from loss of product quality or availability. (*ICH Q9*)

Hazard: The potential source of harm. (*ISO 14971:2000*)

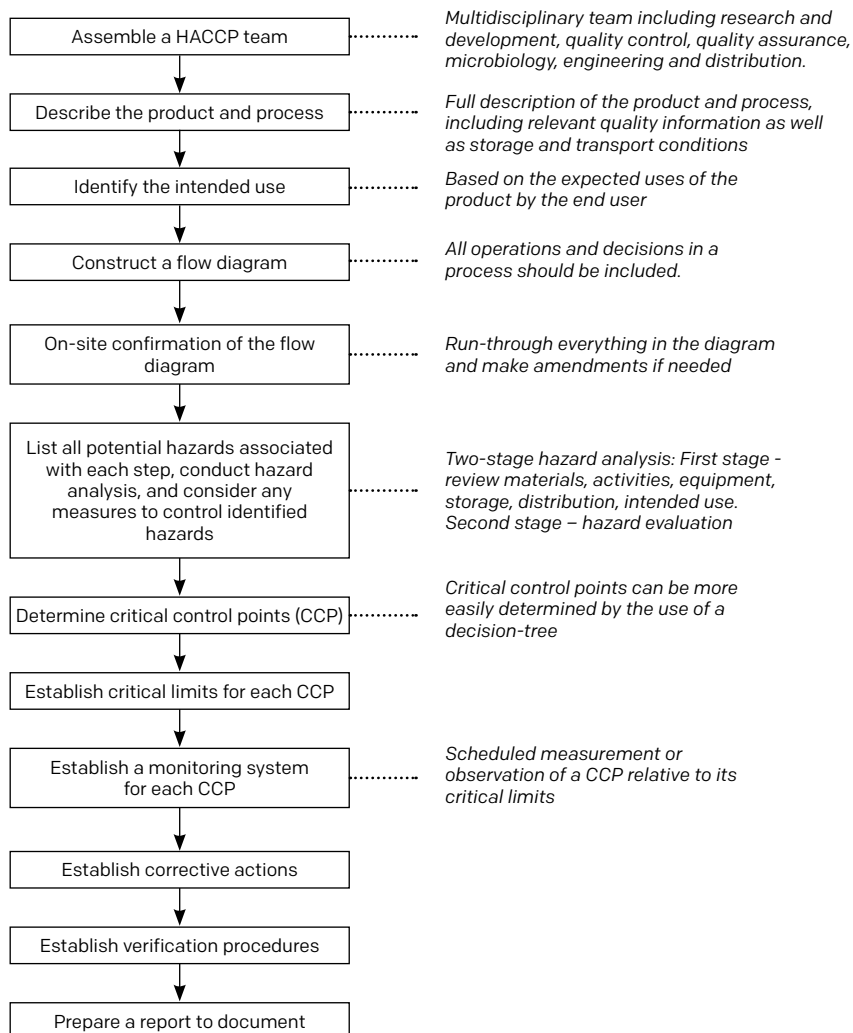
Hazard Analysis and Critical Control Point (HACCP): A systematic, proactive and preventive tool for the identification, assessment and control of safety hazards. It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

WHO recommends the following guidelines in applying the HACCP system:

- Before HACCP is applied to any sector, that sector should be operating in accordance with the principles of good practices and the relevant legislation.
- Management commitment is necessary if an effective HACCP system is to be implemented.
- HACCP should be applied to each specific operation separately.
- CCPs identified in any given example in any reference document (including GMP guidelines) may not be the only ones identified for a specific application or may be of a different nature.
- The HACCP application should be reviewed and necessary changes made when any modification is made in the product or process, or in any step.
- It is important, when applying HACCP, to take into account the nature and size of the operation.
- There should be a HACCP plan. The format of such plans may vary, but they should preferably be specific to a particular product, process or operation. Ge-

neric HACCP plans can serve as useful guides in the development of product and process HACCP plans; however, it is essential that the unique conditions within each facility are considered during the development of all components of the HACCP plan.

HACCP process (Kartoglu)



Hazard and Operability Studies (HAZOP): A qualitative, highly structured inductive tool used to identify, consider, and reduce risks related to the materials, equipment, and operation involved with a process or system. It is usually carried out by a suitably experienced multi-disciplinary team (HAZOP team) during a set of meetings. The amount of information needed to conduct a HAZOP is substantial; it is highly recommended that other risk assessment tools should be use prior to HAZOP to eliminate some of the ore obvious risks. HAZOP is best suited for assessing hazards in facilities, equipment, and processes. It is capable of assessing systems from multiple perspectives such as design, physical and operational environments and operational and procedural controls. In this regard, very detailed process flows and instrumentation drawings or piping are needed to conduct a HAZOP. HAZOP could also be used for new processes and/or for facilities that are being designed.

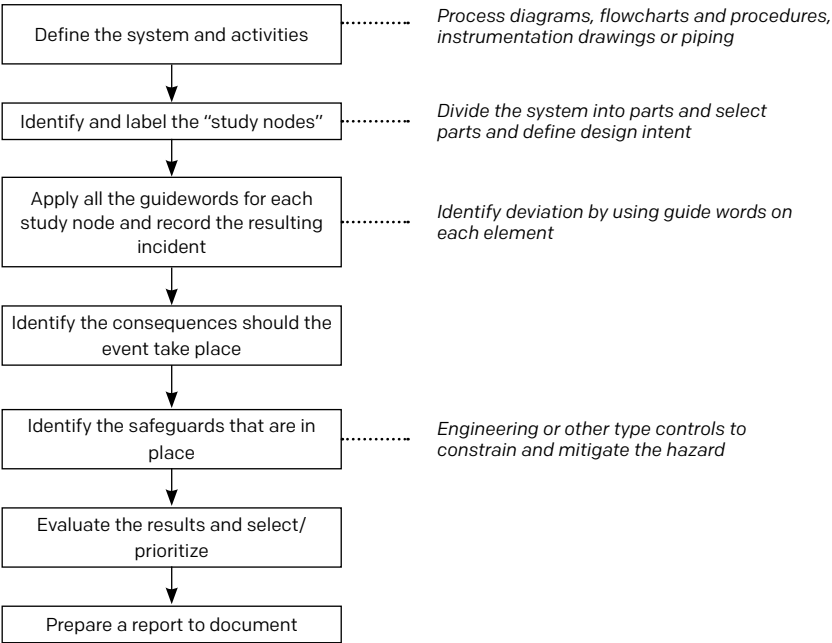
The basis for the HAZOP exercise is a process flow diagram. Within the process flow diagram, “study nodes” need to be identified and labelled. In order to identify deviations, the HAZOP team applies a set of “guide words” to each node. To help discussions, it may also be helpful to use a set of “parameters” which apply to the design intent (e.g., flow, temperature, pressure, composition, level, maintenance). The most frequently used guide words are as follows:

Most frequently used guide words in HAZOP

Guide word	Meaning
No or Not	Complete negation of the design intent
More	Quantitative increase
Less	Quantitative decrease
As well as	Qualitative modification/increase
Part of	Qualitative modification/decrease
Reverse	Logical opposite of design intent
Other than	Complete substitution
Early	Relative to the clock time
Late	Relative to the clock time
Before	Relating to order sequence
After	Relating to order sequence

Following this step, the consequences should be identified should the event take place. Then, engineering or other type controls have to be established to constrain and mitigate a hazard.

HAZOP process (Kartoglu)



An example of HAZOP analysis worksheet (this format to be applied to each defined study node)

No	Guide word	Element	Deviation	Possible cause	Consequences	Safeguards	Comments	Actions required	Actors assigned to
Assign each entry a unique tracking number	Insert deviation guide word used	Describe what the guide word pertains to (material, process step, etc.)	Describe the deviation	Describe how the deviation may occur	Describe what may happen if the deviation occurs	List controls that reduce deviation likelihood or severity	Capture key relevant rationale, assumptions, data, etc.	Identify any hazard mitigation or control actions required	Record who is responsible for actions

Hazard labels: Diamond shape signage indicating hazardous materials applied on the item, container or building where hazardous materials are stored in. The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) is an internationally agreed upon system set to replace the various classification and labelling standards used in different countries. Two sets of pictograms are included within the GHS: first one is for labelling of containers and for workplace hazard warnings and the second one for use during the transport of hazardous materials. The standardized hazard label is composed of a symbol (hazard pictogram), a signal word and a hazard statement.



Class 1: Explosives



Class 2.2: Non-flammable gas



Class 3: Flammable liquids



Class 4: Flammable solids



Class 5.1: Oxidizing agent



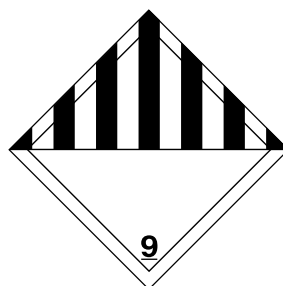
Class 6.2: Biohazard



Class 7: Radioactive



Class 8: Corrosive



Class 9: Miscellaneous

Examples of hazard labels recommended by the UN Model Regulations

Hazard pictograms: See *hazard labels*.

Hazard statement: A statement assigned to a hazard class and category that describes the nature of the hazard of a hazardous product, including, where appropriate, the degree of hazard. (*UN*)

Hazardous materials: See *dangerous goods*.

Heat: A form of energy that flows from a warmer to a cooler environment through either a direct (radiation and/or conduction) or an indirect path (convection).

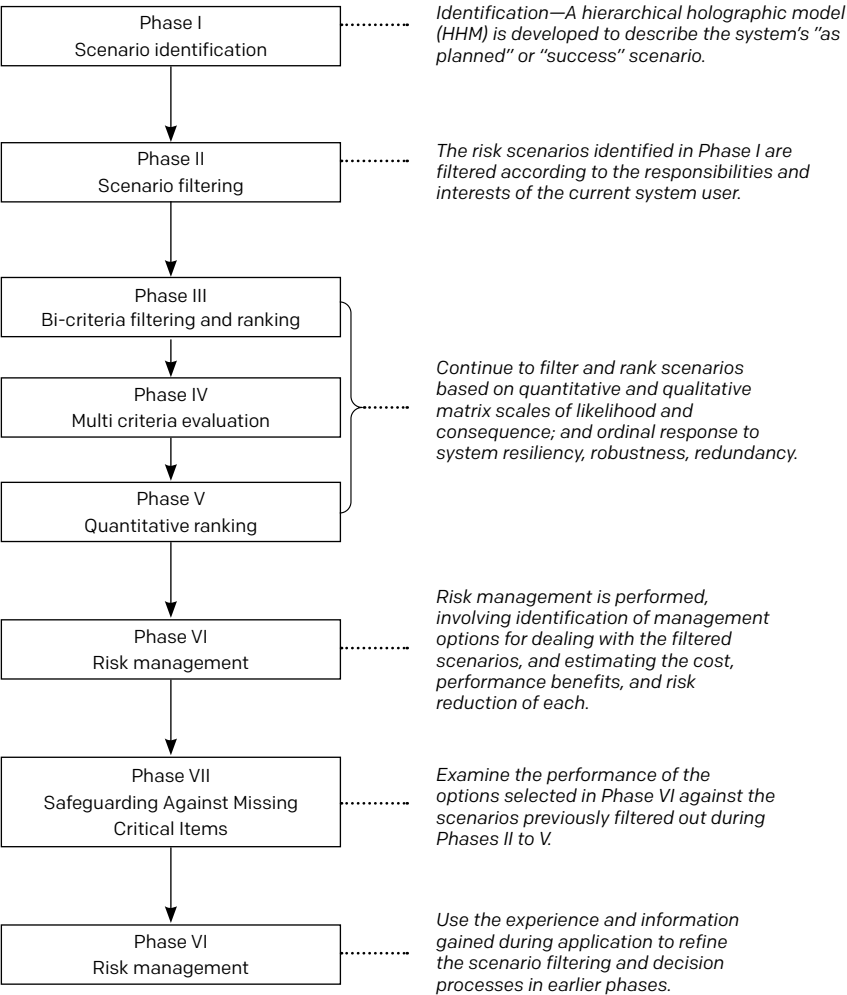
Heat of fusion: The amount of heat that must be added to convert a unit of mass of a solid into a liquid at its melting point temperature, or the amount of heat that must be removed to convert a unit of mass of a liquid into a solid at its freezing point temperature. (*WHO*)

Heat transfer: Exchange of thermal energy between physical systems, depending on the temperature and pressure, dissipating heat. See *conduction*, *convection* and *radiation*.

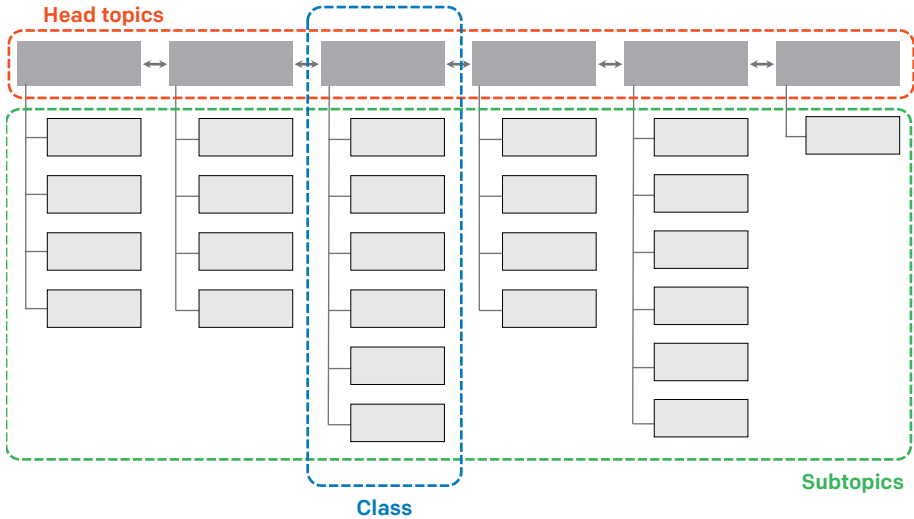
Herbal products: Medicinal products containing, exclusively, plant material and/or vegetable drug preparations as active ingredients. In some traditions, materials of inorganic or animal origin can also be present. (*ICH Q3A/R2*)

Hierarchical holographic modelling (HHM): A methodological framework to identify, prioritize, assess, and manage risk scenarios of a large-scale system. The modelling includes both qualitative and quantitative aspects. It is usually used as the preparatory step to “risk filtering and ranking”. S. Kaplan defines eight phases in HHM which these eight phases reflect a philosophical approach rather than a mechanical methodology. In this philosophy, the filtering and ranking of discrete scenarios is viewed as a precursor to, rather than a substitute for, consideration of the totality of all risk scenarios.

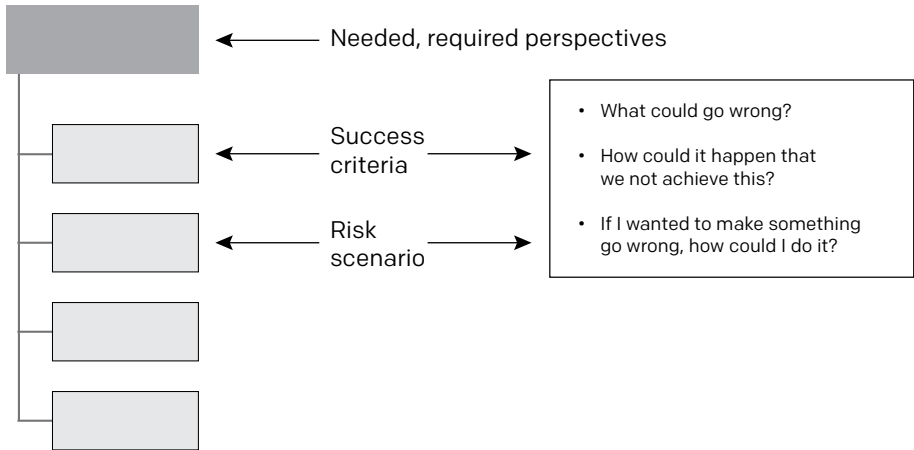
Hierarchical holographic modelling process (after Kaplan, Kartoglu)



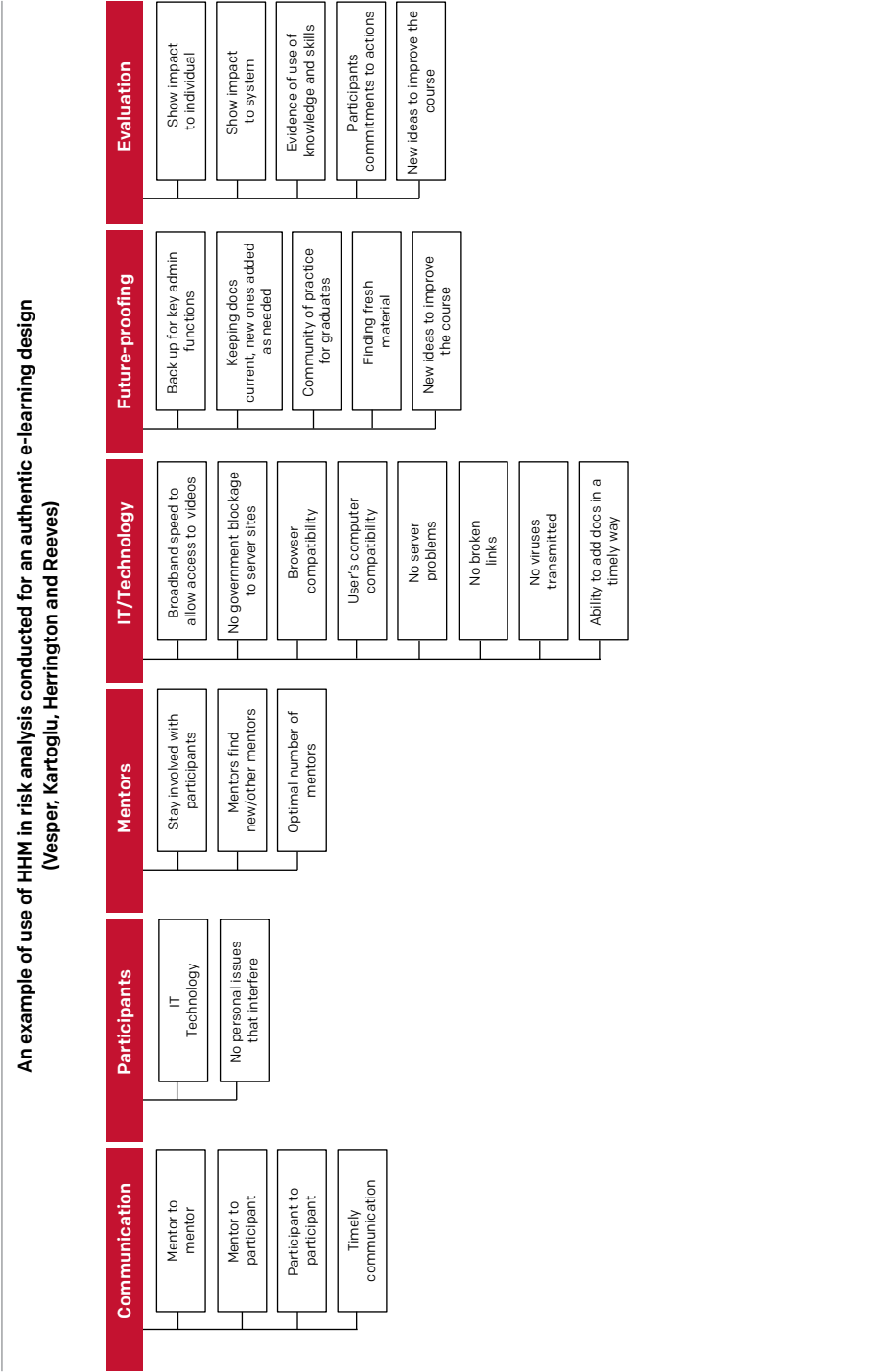
Typical structure HHM illustration (after Kaplan, J.Vesper)



A detailed view of structural components of HHM illustration (J Vesper)



In HHM, success criteria can be studied in order to create risk scenarios.

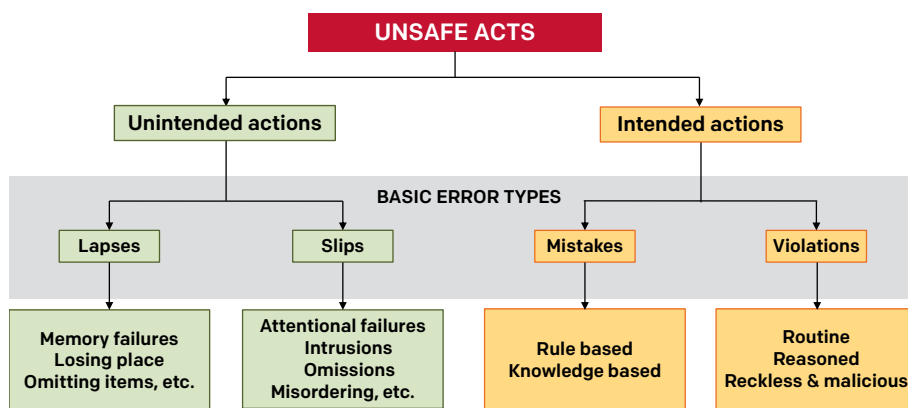


Holdover time: The time in hours during which all points in the vaccine compartment of a vaccine refrigerator remain below +10°C, at the maximum ambient temperature of the temperature zone for which the appliance is rated, after the power supply has been disconnected. For vaccine freezers, the holdover time is the time in hours during which the vaccine compartment remains below -5°C. (WHO)

Host: A person or other living animal, including birds and arthropods, that affords subsistence or lodgment to an infectious agent under natural (as opposed to experimental) conditions. Some protozoa and helminths pass successive stages in alternate hosts of different species. Hosts in which the parasite attains maturity or passes its sexual stage are primary or definitive hosts; those in which the parasite is in a larval or asexual state are secondary or intermediate hosts. A transport host is a carrier in which the organism remains alive but does not undergo development. (WHO)

Human error: All those occasions in which a planned sequence of mental or physical activities fails to achieve its intended outcome, and when these failures cannot be attributed to some change agency (*JT Reason*). Action by human operators can fail to achieve the goal in two different ways: The actions can go as planned, but the plan can be inadequate or the plan can be satisfactory but the performance can be deficient (*E Hollnagel*).

Types of human error (redrawn from JT Reason)



Humidity (relative humidity (RH)): The partial pressure of water vapour in air to the vapour pressure of saturated air at a given temperature. In other words, the RH is the amount of water vapour present, divided by the theoretical amount of moisture that could be held by that volume of air at a given temperature.

Hydrocarbons (HCs): Several hydrocarbons (HCs) have excellent refrigeration fluid properties, zero ODP, and very low global warming potential (GWP). The sole disadvantage of using HCs is their flammability and the risk of explosion. It is recommended that small refrigerators with refrigerant charges of less than 150 g should be preferentially purchased where an option to do so exists. Larger charges can be used, provided safety conditions are met. (*WHO*)

Hydrochlorofluorocarbons (HCFCs): HCFCs are similar to CFCs but contain hydrogen and have a lower ozone-depleting potential. It is now illegal to purchase new refrigerated vehicles that use HCFCs as the refrigerating fluid or those have HCFCs within the insulation in non-Article 5 countries, although they can still be operated using recycled refrigerant. It is recommended that refrigerated vehicles containing HCFCs should not be purchased in Article 5 countries although they can and should be operated until the end of their design life. (*WHO*)

Hydrofluorocarbons (HFCs): HFC refrigerants are composed of hydrogen, fluorine and carbon atoms connected by single bonds; they do not deplete the ozone layer because they do not contain chlorine or bromine. However, they do have a high GWP; some higher than others. Atmospheric concentrations of these gases are rapidly increasing. Currently most refrigerated transport solutions and most fixed refrigeration equipment depend on the use of HFCs and there is no alternative; however HFCs with lower GWP should be considered. Hydrocarbons are recommended for smaller systems. (*WHO*)

Hydrofluoroolefin (HFO): HFO refrigerants are the fourth generation of fluorine-based refrigerants. HFO refrigerants are composed of hydrogen, fluorine and carbon atoms, but contain at least one double bond between the carbon atoms. These compounds have zero ODP and a very low GWP. Therefore these products offer a more environmentally friendly alternative, although there are issues with flammability. (*WHO*)



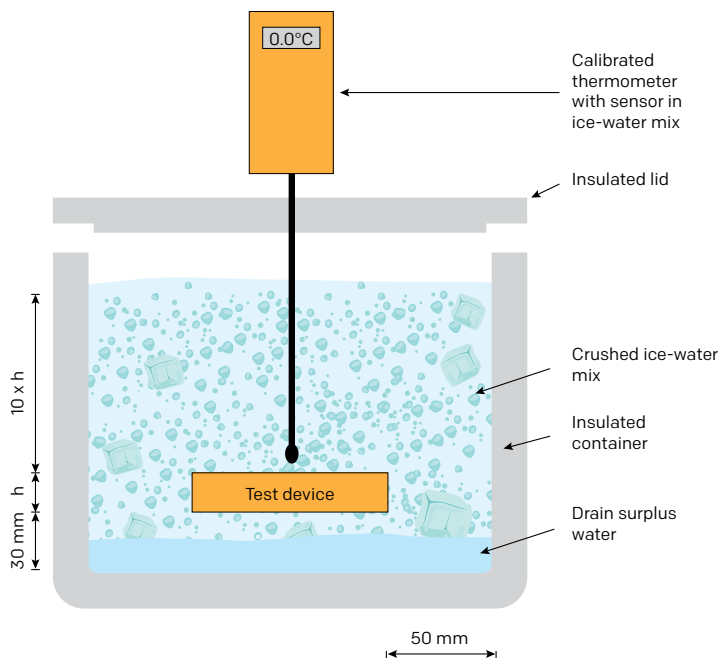
Ice-lined refrigerator: A compression cycle refrigerator with an internal lining surrounding the storage that is filled with ice, cold water, or other coolant. When the electricity supply fails, the ice, cold water or coolant keeps the refrigerator cool for a minimum of 20 hours without power. (WHO)

Ice-pack: A water-pack that has been frozen to a temperature between -5.0°C and -25.0°C before use.

Ice-water bath: A bath of ice and water to maintain a temperature of 0.0°C . The ice-water bath provides an accurate reference temperature at 0.0°C if the melting ice-water mixture is properly set up, handled and maintained. An accurate temperature is achieved by this method because an ice-water mixture in a container which is open to the atmosphere will stabilize at its own “triple point”. At this point all three aggregate states of water coexist: liquid, solid and gaseous. For more physical details refer to *ASTM E563-11*.

Ice-water bath is a relatively simple method for checking the accuracy of temperature control and monitoring devices. The accuracy of the results is dependent upon the use of a high-quality reference thermometer with a valid calibration certificate. (WHO)

Ice-water bath arrangement for checking the accuracy of a temperature control/monitoring device (WHO)



ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH's mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.

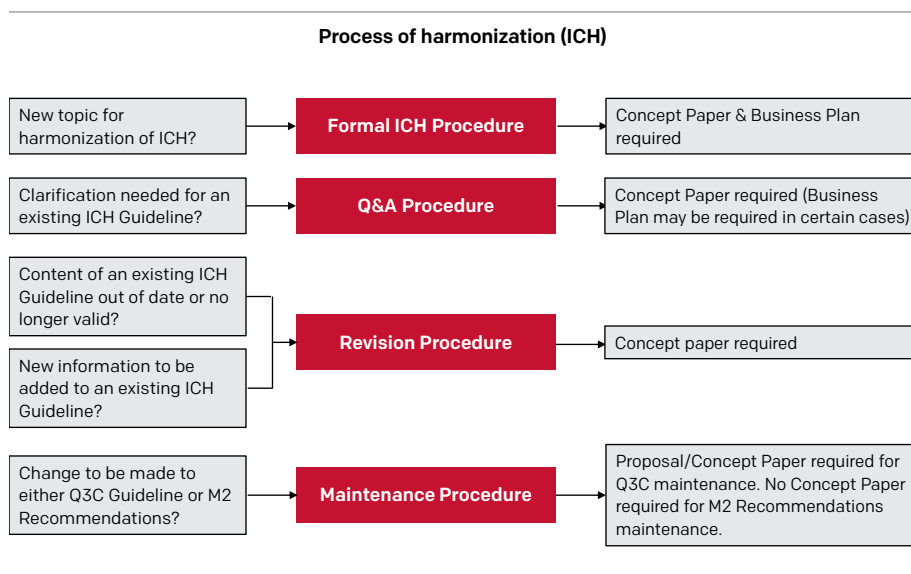
Launched in 1990, ICH is a unique undertaking that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States.

Regulatory harmonisation offers many direct benefits to both regulatory authorities and the pharmaceutical industry with beneficial impact for the protection of public health. Key benefits include: preventing duplication of clinical trials in humans and minimising the use of animal testing without compromising safety and effectiveness; streamlining the regulatory assessment process for new drug applications; and reducing the development times and resources for drug development.

Harmonisation is achieved through the development of ICH Tripartite Guidelines. The Guidelines are developed through a process of scientific consensus with regula-

tory and industry experts working side-by-side. Key to the success of this process is the commitment of the ICH regulators to implement the final Guidelines.

ICH harmonisation activities fall into four categories: Formal ICH Procedure, Q&A Procedure, Revision Procedure and Maintenance Procedure, depending on the activity to be undertaken.



For details see <http://www.ich.org/home.html>

Immune: Protected from or resistant to a disease or infection by a pathogenic organism as a result of the development of antibodies or cell mediated immunity.

Immunity: The state of being immune to or protected from a disease. That resistance usually associated with the presence of antibodies or cells having a specific action on the microorganism concerned with a particular infectious disease or on its toxin. Effective immunity includes both cellular immunity, which is conferred by T-lymphocyte sensitization, and/or humoral immunity, which is based on B-lymphocyte response. Passive immunity is attained either naturally by transplacental transfer from the mother, or artificially by inoculation of specific protective antibodies (from immunized animals, or convalescent hyperimmune serum or immune serum globulin [human]); it is of short duration (days to months). Active humoral Immunity, which usually lasts for years, is attained either naturally by infection with or without clinical manifestations, or artificially by inoculation of the agent itself in killed, modified or variant form, or of fractions or products of the agent.

Immunity (acquired): Immunity resulting from the development of active or passive immunity, as opposed to natural or innate immunity.

Immunity (active): Immunity resulting from the development within the body of antibodies or sensitized T-lymphocytes that neutralize or destroy the infective agent.

Immunity (herd): Immune protection through vaccination of a portion of the population, which may reduce the spread of a disease by limiting the number of potential hosts for the pathogen. (*WHO*)

Card number:

INFANT IMMUNIZATION CARD

NAME OF INFANT:

FEMALE OR MALE:

BIRTH DATE OF INFANT (DAY/MONTH/YEAR):

NAME OF MOTHER:

NAME OF FATHER:

ADDRESS:

Vaccine / Date given

BCG

DTP1

DTP2

DTP3

OPV0

OPV1

OPV2

OPV3

MEASLES

VITAMIN A

HEP B0

HEP B1

HEP B2

HEP B3

TETANUS 1

TETANUS 2

TETANUS 3

TETANUS 4

TETANUS 5

WAS THE INFANT PROTECTED AT BIRTH? * YES / NO

Next appointments (date):

National schedule (example)

Vaccine	Birth	6 weeks	10 weeks	14 weeks	9 months
BCG	x				
Oral Polio	x ^b	x	x	x	
DTP		x	x	x	
Hep B	x ^b	x	x	x	
Measles					x

Notes

^a Ask this question at the DTP 1 contact
^b Birth doses of OPV and HepB are given in some countries

Sample immunization card for infants (WHO)

Immunization anxiety-related reaction: An AEFI arising from anxiety about the immunization. (*WHO*)

Immunization card: A record that contains immunization history and status of a person. The card may be the only record of immunization history and status available for health workers if immunization registers are not well maintained or if clients move from one health facility to another.

Immunization error-related reaction: (formerly *programmatic error*) An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus, by its nature, is preventable. (*WHO*)

Immunization register: An official list or record of immunization services they offer to each infant and to pregnant women.

Village:

Name of health facility:

[illegible]

^a Usually date of first visit ^b DOB: Date of birth ^c Protected at birth from Neonatal Tetanus

Immunization safety: The public health practices and policies dealing with the various aspects of the correct administration of vaccines, focusing on minimizing the risk of transmission of disease with the injection and maximizing the effectiveness of the vaccine. The term encompasses the spectrum of events from proper manufacture to correct administration. (WHO)

Immunogenicity: The capacity of a vaccine to induce antibody-mediated and/or cell-mediated immunity and/or immunological memory. (WHO)

Impact indicator: See *damage indicator*.

Impartial witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. (ICH E6/R1)



An example of impermeable primary container, BCG vaccine from Japan BCG (WHO)

Impermeable containers: Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminium tubes for semisolids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solid dosage forms.

Impurity: Any component of the new drug substance that is not the chemical entity defined as the new drug substance. (ICH Q3A/R2)

Impurity profile: A description of the identified and unidentified impurities present in a new drug substance. (ICH Q3A/R2)

In use: See *utilization period*.

Incidence: The number of persons who fall ill with a certain disease during a defined time period. (WHO)

Incident: An event or circumstance, which could have or did lead to unintended and/or unnecessary harm to a person, and/or a complaint, loss or damage. (Patient Safety International)

Incoterms: Manufacturers and suppliers offer delivery arrangements based on international standard definitions known as Incoterms. A new edition of Incoterms was

published in 2010 and is being phased in. Those below refer to the long-established 2000 edition. It is essential to check which version is being used by the supplier.

Incoterms definitions (WHO)

SERVICE	TERM						
	EXW Ex- Works	FCA Free Carrier	FAS Free Along Ship	FOB Free On Board	FRC Cost and Freight	CIF Cost, Insur- ance and Freight	CPT Car- riage Paid To
Warehouse storage at point of origin	Seller	Seller	Seller	Seller	Seller	Seller	Seller
Warehouse labour at point of origin	Seller	Seller	Seller	Seller	Seller	Seller	Seller
Export packing	Seller	Seller	Seller	Seller	Seller	Seller	Seller
Loading at point of origin	Buyer	Seller	Seller	Seller	Seller	Seller	Seller
Inland freight	Buyer	Buyer	Seller	Seller	Seller	Seller	Seller
Port receiving charges	Buyer	Buyer	Seller	Seller	Seller	Seller	Seller
Forwarders fee	Buyer	Buyer	Seller	Seller	Seller	Seller	Seller
Loading on ocean carrier	Buyer	Buyer	Buyer	Seller	Seller	Seller	Seller
Ocean/Air Freight charges	Buyer	Buyer	Buyer	Buyer	Seller	Seller	Seller
Charges at foreign Port/ Airport	Buyer	Buyer	Buyer	Buyer	Buyer	Buyer	Seller
Customs, Duties & Taxes abroad	Buyer	Buyer	Buyer	Buyer	Buyer	Buyer	Buyer
Delivery charges to final destination	Buyer	Buyer	Buyer	Buyer	Buyer	Buyer	Buyer

Independent Data-Monitoring Committee (IDMC): (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee) An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. (*ICH E6/R1*)

Independent ethics committee (IEC): An independent body (a review board or a committee, institutional, regional or national), constituted of medical, scientific and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and

amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial. Such committees are also known variously as Ethics Committee (EC), Institutional Review Board (IRB), Research Ethics Board (REB), Research Ethics Committee, and other designations. ICH E6/R1 Guideline for Good Clinical Practice (current step 4 version, dated 10 June 1996) also defines the roles and responsibilities of IEC. Responsibilities can be summarized as follows:

- Safeguarding the rights, safety, and well-being of all trial subjects (paying special attention to trials that may include vulnerable subjects).
- Reviewing the proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for either approval/favorable opinion; modifications required for its approval; disapproval/negative opinion; and termination/suspension of any prior approval/favorable opinion.
- Considering the qualifications of the investigator for the proposed trial.
- Conducting continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.
- Reviewing both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects.
- Ensuring that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects.

When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative, the IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials. Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible, the IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations). The IEC may also request more information be given to subjects when, in the judgement of the IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

ICH suggests that the composition of the IEC should include at least five members, with at least one member whose primary area of interest is in a non-scientific area, and at least one member who is independent of the institution/trial site.

Independent variable: Inputs or causes used in an experiment or modelling, or are tested to see if they are the cause. Independent variable is the one that is changed by the experimenter. Independent variable is also known as a “predictor variable”, “regressor”, “controlled variable”, “manipulated variable”, and “explanatory variable”. In graphs, independent variable is positioned in x-axis (horizontal).

Inductive reasoning: Examining specific, individual cases in order to draw a general conclusion. In this regard, inductive reasoning looks for consequences and involves “forward thinking” and projects future outcomes. “What if X situation happens?” is the major question in inductive reasoning. PRA, PHA, FMEA, FMECA, ETA, and HAZOP are inductive risk assessment tools.

Informed consent: A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. (*ICH E6/R1*)

Prior to a subject’s participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject’s legally acceptable representative, and that informed consent was freely given by the subject or the subject’s legally acceptable representative.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed, including all invasive procedures.
- The subject’s responsibilities.
- Those aspects of the trial that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of trial-related injury.

- The anticipated prorated payment, if any, to the subject for participating in the trial.
- The anticipated expenses, if any, to the subject for participating in the trial.
- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- The expected duration of the subject's participation in the trial.
- The approximate number of subjects involved in the trial.

Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies). (*ICH E6/R1*)

Installation qualification (IQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems have been provided and installed in compliance with their design specifications. (*WHO*)

Institutional Review Board (IRB): An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol

and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects. (*ICH E6/R1*)

Instrument: A device that interprets a mechanical, digital or analogue signal generated by a sensor, and converts it into engineering units (e.g., °C, percentage relative humidity, mA) through scaling.

Insulated shipper: A single-use insulated passive container, containing coolant, typically used to distribute TTSPPs by road or air transport. (*WHO*)

Insulated shipping container: Type of packaging used to ship time and temperature sensitive pharmaceutical product (as well as perishables and chemicals). (*WHO*)



EPS puzzle based insulated shipping container (Mediline Isothermal Solutions)

Intention-to-treat principle: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment. (*ICH E9*)

Interim clinical trial/study report: A report of intermediate results and their evaluation based on analyzes performed during the course of a trial. (*ICH E6/R1*)

Intermediate vaccine store: A secondary store or substore that receives vaccine either from a primary vaccine store or another intermediate vaccine store and distributes vaccine to lower levels. (*WHO*)

Intermediates: Material produced during the manufacturing process, which is not yet in the final product, but whose manufacture is critical for the successful production of the actual vaccine. As part of quality assessment, both quantifiable and qualitative parameters of an intermediate should be defined and specifications established to determine the successful completion of the manufacturing step prior to continuation of the manufacturing process. This includes material that may undergo further molecular modification or be held for an extended period of time prior to further processing. (*WHO*)

Internal distribution: Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e., all internal transport from the manufacturing plant to the

packaging plant and onwards to warehouses and distribution centres). Contrast with *external distribution*. (WHO)



International Clinical Trials Registry Platform (ICTRP): A global initiative aiming to make information about all clinical trials involving human beings publicly available. It was established in 2006 in response to demand from countries through the World Health Assembly for “a voluntary platform to link clinical trials registers in order to ensure a single point of access and the unambiguous identification of trials with a view to enhancing access to information by patients, families, patient groups and others”. The Secretariat

of the ICTRP is housed by the World Health Organization in its headquarters in Geneva. WHO regards trial registration as the publication of an internationally-agreed set of information about the design, conduct and administration of clinical trials. These details are published on a publicly-accessible website managed by a registry conforming to WHO standards. For further details visit <http://goo.gl/3pWqM>



International Federation of Pharmaceutical Manufacturers and Associations (IFPMA): Founded in 1968, the IFPMA is a global, non-profit, nongovernmental organization with members across the globe and a secretariat based in Geneva, Switzerland. The IFPMA represents the research-based pharmaceutical industry, including the biotechnology and vaccine sectors. The IFPMA advocates policies that encourage discovery of and access to life-saving and life-enhancing medicines to improve the health of people everywhere. For details visit <http://www.ifpma.org/>

International Medical Products Anti-Counterfeiting Taskforce (IMPACT): A taskforce administered by WHO in 2006, aiming to build coordinated networks across and between countries in order to halt the production, trading and selling of fake medicines around the globe. IMPACT is a partnership comprised of all the major anti-counterfeiting players, including: international organizations, non-governmental organizations, enforcement agencies, pharmaceutical manufacturers associations and drug and regulatory authorities. (WHO)

International nonproprietary name (INN): An official generic name given to a pharmaceutical drug or active ingredient. INN facilitates the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name. (WHO)

International standards for clinical trial registers: Standards developed as part of the programme of work of the World Health Organization's International Clinical Trials Registry Platform. The specific, detailed standards further define the requirements of each registry criterion. The standards were considered by the registries participating in the 1st Meeting of the ICTRP Registry Network held in WHO Headquarters, Geneva, Switzerland 11-12 November 2010, and then finalized. See full text at <http://goo.gl/T36HFK>

Inventory control card: An individual stock keeping card that keeps information about all batches of a product. One inventory control card should be kept for each product. For example, for a DTP vaccine of three different batches, there should be three batch cards and one inventory control card. In the inventory control card, total quantity in hand of DTP vaccines, as well as the total losses and adjustments regardless of the batch numbers and locations of the products will be seen. Inventory control card is a summary of the batch cards for a product. (WHO)

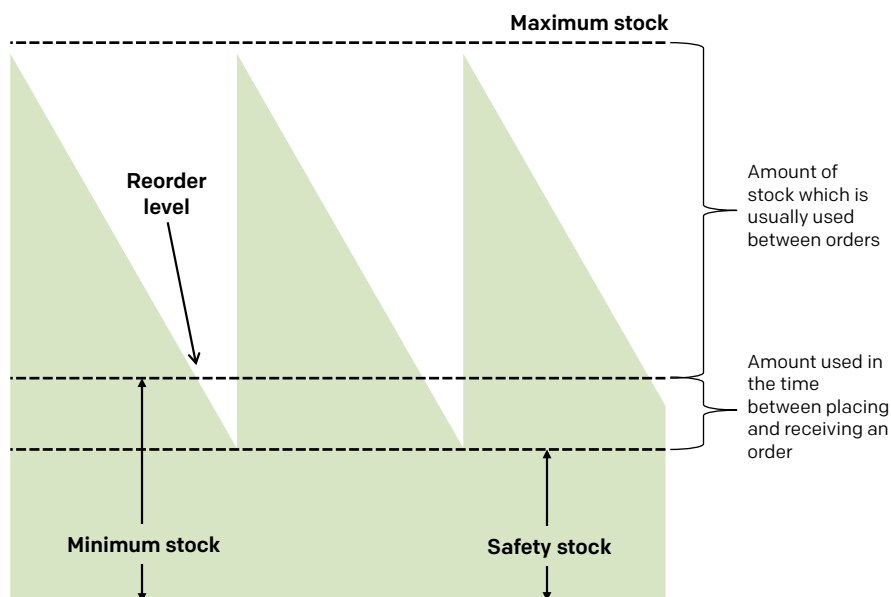
Store name:	<input type="text"/>	Most recent AMC:	<input type="text"/>
Product name:	<input type="text"/>	Vial size:	<input type="text"/>
		AMC calculation date:	<input type="text"/>

[illegible]

Inventory control system: A process for managing and locating objects or materials. Minimum/maximum (min/max) inventory control system is recommended in pharmaceutical stock management in which, each organizational level of the programme is assigned maximum and minimum levels for its supplies. Using a min/max inventory control system will help managers to prevent both over-stocking (which leads to higher wastage) and shortages or stock outs of pharmaceutical product and other related supplies. (WHO)

Inventory turnover: A measure of the number of times inventory is sold or used in a time period such as a year. The equation for inventory turnover equals the cost of goods sold divided by the average inventory. Inventory turnover is also known as inventory turns, stockturn, stock turns, turns, and stock turnover. (WHO)

Stock movement and relation between minimum, maximum and safety stock levels (WHO)



Investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. (ICH E6/R1)

Investigator: A qualified scientist who undertakes scientific and ethical responsibility, either on his/her own behalf or on behalf of an organization/ firm, for the ethical and scientific integrity of a research project at a specific site or group of sites. In some instances a coordinating or principal investigator may be appointed as the responsible leader of a team of sub-investigators. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IEC, and/or the regulatory authority(ies). (*WHO*) See also *sub-investigator*.

Investigator's brochure (IB): A compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects (*ICH E6/R1*). Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. ICH section 7 of the E6/R1 Guideline for Good Clinical Practice (Current Step 4 version, dated 10 June 1996) delineates the minimum information that should be included in an IB and provides suggestions for its layout. Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IECs.

<p>7.4 APPENDIX 1:</p> <p>TITLE PAGE (Example)</p> <p>SPONSOR'S NAME</p> <p>Product:</p> <p>Research Number:</p> <p>Name(s): Chemical, Generic (if approved) Trade Name(s) (if legally permissible and desired by the sponsor)</p> <p style="text-align: center;">INVESTIGATOR'S BROCHURE</p> <p>Edition Number:</p> <p>Release Date:</p> <p>Replaces Previous Edition Number:</p> <p>Date:</p>	<p>TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)</p> <ul style="list-style-type: none"> - Confidentiality Statement (optional) - Signature Page (optional) 1 Table of Contents 2 Summary 3 Introduction 4 Physical, Chemical, and Pharmaceutical Properties and Formulation 5 Nonclinical Studies 5.1 Nonclinical Pharmacology 5.2 Pharmacokinetics and Product Metabolism in Animals 5.3 Toxicology 6 Effects in Humans 6.1 Pharmacokinetics and Product Metabolism in Humans 6.2 Safety and Efficacy 6.3 Marketing Experience 7 Summary of Data and Guidance for the Investigator <p>NB: References on</p> <ul style="list-style-type: none"> 1. Publications 2. Reports <p>These references should be found at the end of each chapter</p> <p>Appendices (if any)</p>
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**Example of title page and table of contents for investigator brochure
as suggested by the ICH E6/R1**



A 20-foot (6.09 m) long shipping container. Each of the eight corners has an essential twist lock fitting for hoisting, stacking, and securing (Eugene Sergeev, Shutterstock)

ISO container: Large standardized shipping container, designed and built for intermodal freight transport, meaning these containers can be used across different modes of transport - from ship to rail to truck - without unloading and reloading their cargo. Intermodal containers are primarily used to store and transport materials and products efficiently and securely in the global containerized intermodal freight transport system, but smaller numbers are in regional use as well.

These containers are known under a number of names, such as simply container, cargo or freight container, shipping, sea or ocean container, container van or Conex box.

A few relevant ISO series standards include:

- ISO 6346:1995 Freight containers - Coding, identification and marking
- ISO 668:2013 Series 1 freight containers - Classification, dimensions and ratings
- ISO 1161:1984 Series 1 freight containers - Corner fittings - Specification
- ISO 1496-1:2013 Series 1 freight containers - Specification and testing - Part 1: General cargo containers for general purposes

Weights and dimensions of the most common standardized types of containers are given below. Values vary slightly from manufacturer to manufacturer, but must stay within the tolerances dictated by the standards.

		20' container		40' container		40' high-cube container		45' high-cube container	
		imperial	metric	imperial	metric	imperial	metric	imperial	metric
external dimensions	length	19' 10.5"	6.058 m	40' 0"	12.192 m	40' 0"	12.192 m	45' 0"	13.716 m
	width	8' 0"	2.438 m	8' 0"	2.438 m	8' 0"	2.438 m	8' 0"	2.438 m
	height	8' 6"	2.591 m	8' 6"	2.591 m	9' 6"	2.896 m	9' 6"	2.896 m
interior dimensions	length	18' 8 ¹³ / ₁₆ "	5.710 m	39' 5 ⁴⁵ / ₆₄ "	12.032 m	39' 4"	12.000 m	44' 4"	13.556 m
	width	7' 8 ¹⁹ / ₃₂ "	2.352 m	7' 8 ¹⁹ / ₃₂ "	2.352 m	7' 7"	2.311 m	7' 8 ¹⁹ / ₃₂ "	2.352 m
	height	7' 9 ⁵⁷ / ₆₄ "	2.385 m	7' 9 ⁵⁷ / ₆₄ "	2.385 m	8' 9"	2.650 m	8' 9 ¹⁵ / ₁₆ "	2.698 m
door aperture	width	7' 8 ¹ / ₈ "	2.343 m	7' 8 ¹ / ₈ "	2.343 m	7' 6"	2.280 m	7' 8 ¹ / ₈ "	2.343 m
	height	7' 5 ³ / ₄ "	2.280 m	7' 5 ³ / ₄ "	2.280 m	8' 5"	2.560 m	8' 5 ⁴⁹ / ₆₄ "	2.585 m
internal volume		1,169 ft ³	33.1 m ³	2,385 ft ³	67.5 m ³	2,660 ft ³	75.3 m ³	3,040 ft ³	86.1 m ³
maximum gross weight		66,139 lb	30,400 kg	66,139 lb	30,400 kg	68,008 lb	30,848 kg	66,139 lb	30,400 kg
empty weight		4,850 lb	2,200 kg	8,380 lb	3,800 kg	8,598 lb	3,900 kg	10,580 lb	4,800 kg
net load		61,289 lb	28,200 kg	57,759 lb	26,600 kg	58,598 lb	26,580 kg	55,559 lb	25,600 kg

ISO pallets: The International Organization for Standardization (ISO) sanctions six pallet dimensions, detailed in *ISO Standard 6780: Flat pallets for intercontinental materials handling—Principal dimensions and tolerances*:

Dimensions (W × L) millimetres	Dimensions (W × L) inches	Wasted floor, ISO container	Region most used in
1016 × 1219	40.00 × 48.00	3.7% (20 pallets in 40 ft ISO)	North America
1000 × 1200	39.37 × 47.24	6.7%	Europe, Asia; similar to 40" × 48".
1165 × 1165	45.9 × 45.9	8.1%	Australia
1067 × 1067	42.00 × 42.00	11.5%	North America, Europe, Asia
1100 × 1100	43.30 × 43.30	14%	Asia
800 × 1200	31.50 × 47.24	15.2%	Europe; fits many doorways

Issue voucher: Transaction record that lists the items and quantities of products issued to a facility.

A sample issue voucher (WHO)

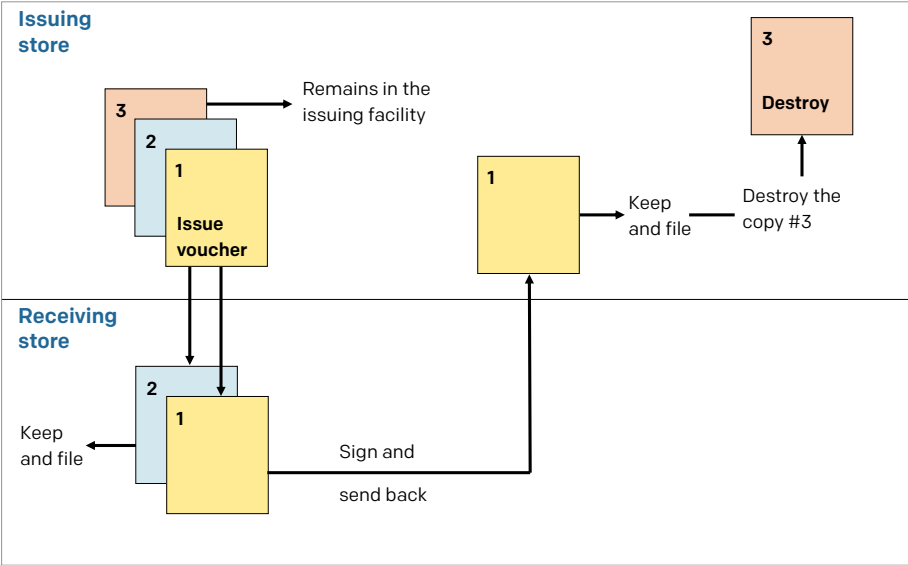
Voucher no:	<input style="width: 90%;" type="text"/>	Issuing store:	<input style="width: 90%;" type="text"/>	Ship to:	<input style="width: 90%;" type="text"/>
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Article no	Commodity name	Batch number	Expiry date	ISSUE			RECEIVE			Remarks
				Freeze indicator	VVM status	Amount (doses)	Freeze indicator	VVM status	Amount (doses)	
A	B	C	D	E	F	G	H	I	J	K
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
ISSUE						RECEIVE				

<p>Approved by</p> <p>Name: <input style="width: 80%;" type="text"/></p> <p>Title: <input style="width: 80%;" type="text"/></p> <p>Signature: <input style="width: 80%;" type="text"/> Date: <input style="width: 20%;" type="text"/></p> <p>Shipped by</p> <p>Name: <input style="width: 80%;" type="text"/></p> <p>Title: <input style="width: 80%;" type="text"/></p> <p>Signature: <input style="width: 80%;" type="text"/> Date: <input style="width: 20%;" type="text"/></p>	<p>Received by</p> <p>Name: <input style="width: 80%;" type="text"/></p> <p>Title: <input style="width: 80%;" type="text"/></p> <p>Signature: <input style="width: 80%;" type="text"/></p>
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An issue voucher should be completed in three copies. The issuing facility completes the date and quantities issued, signs the record, and sends the top two (1 and 2) copies to the receiving facility along with the supplies. The bottom copy (3) is remained in the issuing facility. The receiving facility verifies the quantity received, signs the form, and sends the top copy (1) back and keeps the middle copy (2) for its records. The top copy (1) arrives at the issuing facility, which issuing facility then disposes of copy (3) and keeps the top copy (1) for its files. At the end, each of the facilities ends up with a completed copy of the issue voucher for filing (see figure).

Flow diagram of issue voucher (Kartoglu)



Issues data: Information on the quantity of goods shipped from one level of a system to another. See also *consumption data*.



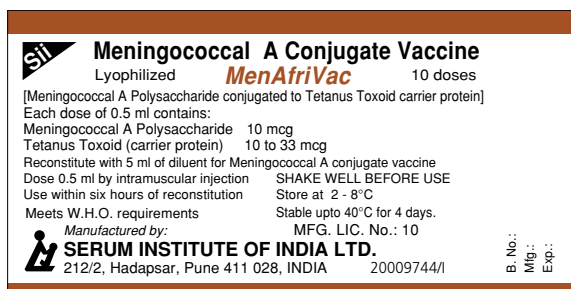
Key fob: A small security device with built-in authentication used to control entry to a building and/or entry through internal doors within a building. (*WHO*)

Key operating parameters: Parameters that must be maintained in order to process or produce products with consistent quality attributes and those that may have an impact on the proper operation of the equipment. (*ICH Q10*)



Label: All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information (*WHO*):

- the name of the drug product;
- a list of the active ingredients (if applicable, with the International Nonproprietary Names (INNs)), showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, mass or volume;
- the batch number assigned by the manufacturer;
- the expiry date in an uncoded form;
- any special storage conditions or handling precautions that may be necessary;
- the directions for use, and any warnings and precautions that may be necessary;
- the name and address of the manufacturer or the company or person responsible for placing the product on the market.



An example of a label
(MenAfriVac, Serum Institute of India Ltd.)

Written labels on the packaging permit the follow-up of a specific medicinal product by means of the batch number on the labels. It must be possible to follow the route of distribution of a product from the manufacturing process to its administration to the patient with the aim of locating and identifying products that are of potential risk (e.g. blood prod-

ucts, blood-derived products). They also mask the real identity of the medicinal product in clinical studies. This is extremely important in clinical trials in determining the real efficacy of a medicinal product in blinded studies. If the identity is masked by a code, it must be possible to disclose it at any time in a medical emergency. (WHO)

Labelling (for APIs and FPPs): The action involving the selection of the correct label, with the required information, followed by line-clearance and application of the label. A storage statement should be established for display on the label based on the stability evaluation of the API. Where applicable specific instructions should be provided, particularly for APIs that cannot tolerate freezing or excursions in temperature. Terms such as “ambient conditions” or “room temperature” should be avoided. (WHO)

Recommended labelling statements for active pharmaceutical ingredients and finished pharmaceutical products (WHO)

Testing condition under which the stability of the API has been demonstrated	Recommended labelling statement ^a
25°C/60% RH (long-term) 40°C/75% RH (accelerated)	“Do not store above 25°C”
25°C/60% RH (long-term) 30°C/65% RH (intermediate, failure of accelerated)	“Do not store above 25°C” ^b
30°C/65% RH (long-term) 40°C/75% RH (accelerated)	“Do not store above 30°C” ^b
30°C/75% RH (long-term) 40°C/75% RH (accelerated)	“Do not store above 30°C”
5°C ± 3°C	“Store in a refrigerator (2°C to 8°C)”
-20°C ± 5°C	“Store in freezer”

^a During storage, shipment and distribution of the API, the current good trade and distribution practices (GTDP) for pharmaceutical starting materials are to be observed..

^b “Protect from moisture” should be added as applicable.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in the below Table.

Additional labelling statements for use where the result of the stability testing demonstrates limiting factors (WHO)

Limiting factors	Additional labelling statement, where relevant
FPPs that cannot tolerate refrigeration	"Do not refrigerate or freeze" ^a
FPPs that cannot tolerate freezing	"Do not freeze" ^a
Light-sensitive FPPs	"Protect from light"
FPPs that cannot tolerate excessive heat, e.g., suppositories	"Store and transport not above 30°C"
Hygroscopic FPPs	"Store in dry condition"

^a Depending on the pharmaceutical form and the properties of the FPP, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g., liquids and semi-solids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

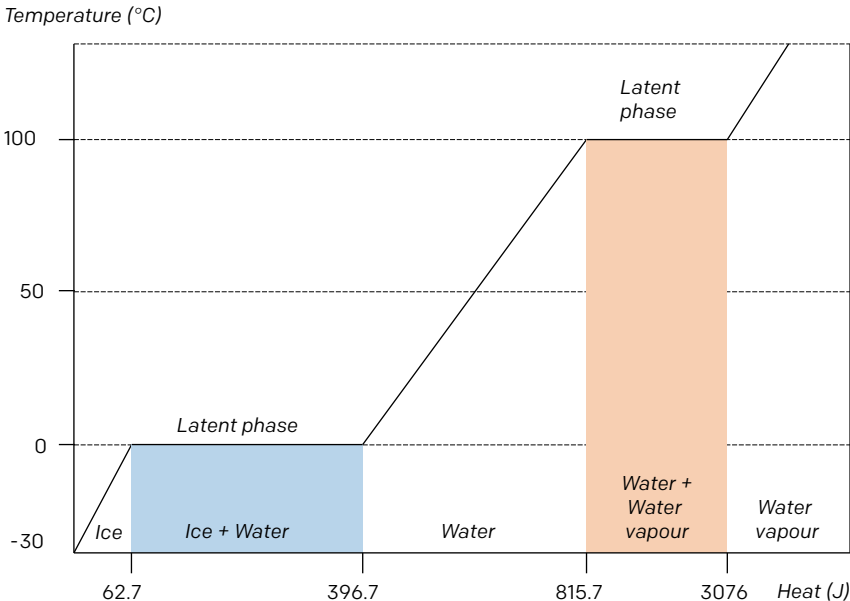
Lanes: Transport routes from a point of origin to a destination.

Last mile: Last mile is the final leg of the supply chain that is between a service point and a customer, as it is often the least efficient link in the supply chain. By definition, it does not need to be a mile. For example, when you order a product from an online distributor located in another country and the product is sent directly to you, this is the last mile. In another example, when you ask your pharmacy for your prescription to be delivered to your home, this is the last mile. In health services, two approaches are used in last mile; active and passive. Immunization programme uses an active approach, when a child does not come for a scheduled vaccination session, the programme follows the person to reach and vaccinate. On the contrary, retail pharmacies use passive approach, they wait for patients to come with their prescriptions.

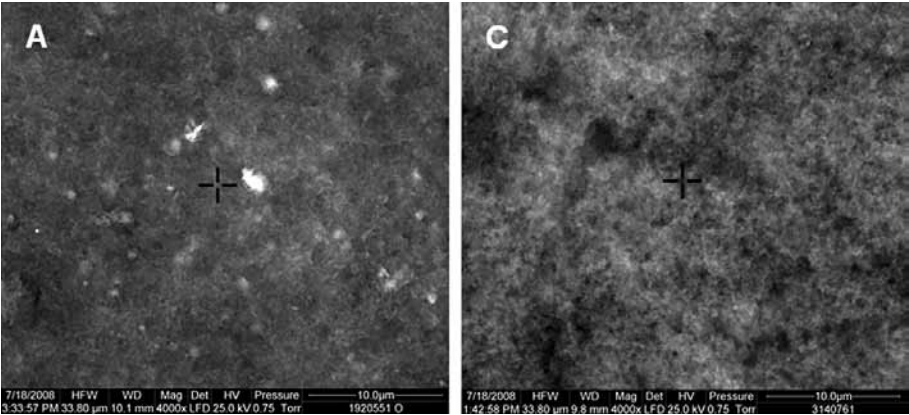
Latent heat: Characteristic amount of energy absorbed or released by a substance during a change in its physical state that occurs without changing its temperature. The latent heat associated with melting a solid or freezing a liquid is called the heat of fusion; that associated with vaporizing a liquid or a solid or condensing a vapour is called the heat of vaporization. (*Encyclopædia Britannica*)

While ice melts, it remains at 0°C, and the liquid water that is formed with the latent heat of fusion is also at 0°C. The latent heat is the major motive in using ice-packs/PCMs for passive cooling.

Phase changes of water as heat is added or removed (Kartoglu)



Lattice: Mesh like structure of bonds between aluminum adjuvant and the antigen in freeze-sensitive vaccines. The lattice is affected by freezing. Once frozen, the bond between the aluminum adjuvant and the antigen gets broken, and separated aluminum tends to form granules and conglomerates. See also *shake test*.



Scanning electron micrographs of lattice structure in non-frozen HepB (A) and DTP-HepB (C) vaccines (kept at +2°C to +8°C at all times)

Law: Any rule or standard of conduct that is recognized as binding and enforceable within a particular governmental system. Laws can exist in a variety of forms, including constitutions, statutes, administrative regulations, court decisions, executive orders, and other instruments. (WHO)

Lead time: The time between when new stock is ordered and when it is received and available for use. Lead time varies, depending on the system, speed of deliveries; availability and reliability of transport, and sometimes, weather. (WHO)

Lean manufacturing: A systematic method for the elimination of waste within a manufacturing system. Essentially, lean is centred on making obvious what adds value by reducing everything else.

Lean thinking: A term created by James P. Womack and Daniel T. Jones and is a business methodology aiming to provide a new way to think about how to organize human activities to deliver more benefits to society and value to individuals while eliminating waste. The basic insight of lean thinking is that if you train each staff to identify wasted time and effort in their own job and to better work together to improve processes by eliminating such waste, the resulting enterprise will deliver more value at less expense while developing every employee's confidence, competence and ability to work with others.



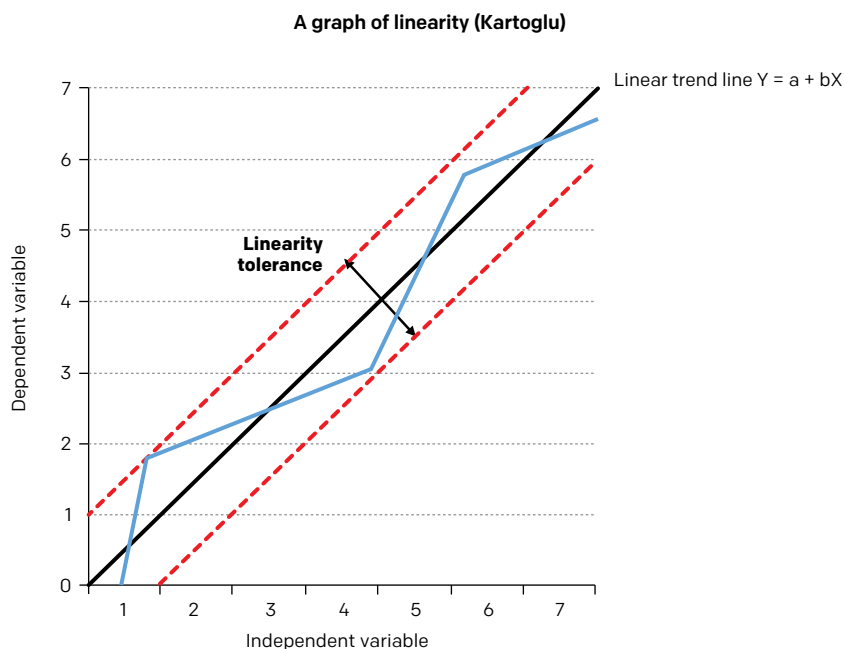
Daniel T. Jones and James P. Womack

Legal manufacturer: The producer of the drug product or vaccine. A legal manufacturer is the natural or legal person with responsibility for the design, manufacture, packaging and labeling of a product or device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party. (WHO)

Legally acceptable representative: An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. (*ICH E6/R1*)

Lifecycle: All phases in the life of a product from the initial development through marketing until the product's discontinuation. (*ICH Q8*)

Linearity: A relationship of direct proportionality that, when plotted on a graph, traces a straight line ($Y = a + bX$). In linear relationships, any given change in an independent variable will always produce a corresponding change in the dependent variable.



Long-term stability studies: Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an API or FPP, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the re-test period or the shelf-life, to confirm the projected re-test period and shelf-life, and to recommend storage conditions. For APIs with a proposed re-test period or shelf-life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year, and annually thereafter throughout the proposed re-test period or shelf-life. (*WHO*)

Loss report: Record of loss items issued for damaged, expired products as well as for missing inventory. Loss report is a critical report for accountability purposes. (WHO)

A sample loss report (UNICEF)

Loss report			Serial number		
Issuing office					
Issued by		Title		Date and signature	
Approved by		Title		Date and signature	
Nature of loss					
<input type="checkbox"/> Damaged in store		<input type="checkbox"/> Damaged by heat		<input type="checkbox"/> Expired	
<input type="checkbox"/> Damaged in transit		<input type="checkbox"/> Freezing		<input type="checkbox"/> Missing inventory	
		<input type="checkbox"/> Other			
No	Item description	Unit size	Quantity to be disposed of	Remarks	
Recommendations of corrective actions and disposal					
Property Board submission					
List of documents attached to the report (photos, claim, laboratory analysis, batch and expiry dates...)					
ORIGINAL COPY 1 COPY 2 COPY 3					

Losses: The quantity of stock removed from the pipeline for any reason other than consumption by clients (e.g., expiration and damage).

Lot: See *batch*.

Lot number: See *batch number*.

Lot release: The process of evaluating each individual lot of a licensed product before giving approval for its release onto the market (*WHO*). This process is carried out for vaccines and other biologicals in most countries. General practices of release involves the review of manufacturer's production data and quality control test results (product summary protocol) by the national regulatory authorities (NRA) and national control laboratory (NCL)s. This may or may not be supplemented by laboratory testing by the national control laboratory, or by an agency or contracted laboratory performing tests for the NRA. Lot release of vaccines by, as a minimum, review of a summary protocol and access to a laboratory are two of the essential functions of a NRA for assuring the quality of vaccines used in the immunization programme as defined by *WHO*.

Lot release certificate (LRC): A certificate issued by the manufacturing country's national regulatory authority for every single batch of a product to be marketed, indicating that the batch of product has been examined and tested by the NRA/NCL and is in compliance with the approved specifications laid down in the relevant monographs of the pharmacopeia and in relevant marketing authorization (*WHO*). All shipments should be accompanied by the LRC issued by the regulatory authority of the producing country. In addition to the lot release certificates, producers usually include their own internal release documents with the shipping documents. At country level these documents are sometimes confused with the official lot release certificates issued by the NRA of the producing country. Manufacturers' release documents and any other papers that may accompany a shipment do not replace and are not a substitute for the official lot release certificates issued by the NRA of the producing country.

Lot size stock: See *working stock*.

(To be completed by the national control authority of the country where the vaccines have been manufactured, and to be sent by the vaccine manufacturer to UNICEF.)

The following lots of¹ vaccine produced by² in³ whose numbers appear on the labels of the final containers meet all national requirements.⁴ Part A⁵ of Requirements for Biological Substances No.⁶ (Requirements for¹, published in 19..... (if applicable, revised 19....., addendum 19.....)) and Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories, published in 1959; revised 19.....)⁷.

Lot No.	Expiry date	Lot No.	Expiry date
.....
.....
.....
.....

As a minimum, this certificate is based on examination of the manufacturing protocol. The Director of the National Control Laboratory (or Authority as appropriate)⁸

Named (typed)

Signature

Date

¹ Indicate type of vaccine (measles, oral poliomyelitis, tetanus, diphtheria-tetanus, diphtheria-pertussis-tetanus, BCG).

² Name of manufacturer.

³ Country

⁴ If any national requirements are not met, specify which one(s) and indicate why release of the lot(s) has nevertheless been authorized by the national control authority.

⁵ With the exception of the provisions on shipping, which the national control authority may not be in a position to control.

⁶ Indicate the reference number of the relevant Requirements for Biological Substances published by WHO.

⁷ These requirements were revised in 1965; a further revision is in preparation for consideration

⁸ Or his or her representative.

**Model certificate for the release of vaccines
acquired by United Nations agencies
(revised 1988)**

M

Main equipment: Major equipment to be qualified.

Maintenance management: The administrative, financial, and technical framework for assessing and planning building maintenance operations on a scheduled basis; a subset of facility management. (*WHO*)

Management Review of Process Performance and Product Quality: A review to provide assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review. (*ICH Q10*)

Application of management review of process performance and product quality throughout the product lifecycle (ICH Q10)

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale.	Management review should be a structured system, as described above, and should support continual improvement.	Management review should include such items as product stability and product quality complaints.

Mandatory signs: See *precautionary pictograms*.

Mapping: Documented measurement of the temperature and/or relative humidity distribution within a storage area, including identification of hot and cold spots. (*WHO*)

Marketing authorization: An official document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g., “The product(s) must conform with all the details provided in your application and as modified in subsequent correspondence”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be “registered” or to “have registration”. Market authorization may occasionally also be referred to as a licence or product licence. (*WHO*)

Marketing partner: Marketing partner is a commercial entity with which another commercial entity has some sort of alliance. This relationship may be a contractual, exclusive bond in which both entities commit not to ally with third parties. (This is sometimes also called “co-commercialization”.) For example, Company A and Company B both markets the drug X.

Masking: See *blinding*.

Master file: A master file is a dataset that is:

- submitted by someone other than a finished product applicant, e.g. the supplier of an active ingredient or the supplier of a packaging component;
- a common feature of more than one product, e.g. sterility test procedures; or
- some other matter that is conveniently dealt with by means of a master file.

An applicant for a new marketing authorization or for a variation may make reference to a master file, but must have the permission of the person or company that submitted the master file. (*WHO*)

Master formula: A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including in-process controls. (*WHO*)

Matrixing: The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same FPP should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems. (ICH Q1D)

Maximum payload: The amount of product intended to be shipped with the most amount of thermal mass. (WHO)

Maximum rated ambient temperature: The highest constant ambient temperature at which a WHO prequalified vaccine refrigerator can maintain the vaccine storage compartment between +2°C and +8°C.

Maximum stock level: The largest amount of stock the programme should have in stock, usually expressed as the number of months of supply. It is the minimum stock plus that amount of stock used between orders. The maximum stock level is set to guard against oversupply which results in losing products to expiration before they can be used. (WHO)

Mean kinetic temperature (MKT): A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation. (ICH Q1A/R2)

MKT is not helpful if supporting stability data of the product is not available. In addition, since excursions at temperatures below freezing point may result in phase change of the material, the use of MKT will produce a false security. The impact of such temperature excursions to product will not be known unless freeze-thaw studies have been conducted. In this regard, the higher and lower temperature control limits should be based on kinetic and stability data of the product.

Medical care of trial subjects: A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject

when medical care is needed for intercurrent illness(es) of which the investigator becomes aware. (*ICH E6/R1*)

Medicinal product: See *pharmaceutical product*.

Medicine: Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. (*WHO*)

Medicines regulatory authority: A national body that administers the full spectrum of medicines regulatory activities, including at least all of the following functions (*WHO*):

- marketing authorization of new products and variation of existing products;
- quality control laboratory testing;
- adverse drug reaction monitoring;
- provision of medicines information and promotion of rational use of medicines;
- good manufacturing practice (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;
- enforcement operations;
- monitoring of medicine utilization.

Meta-analysis: The formal evaluation of the quantitative evidence from two or more trials bearing on the same question. This most commonly involves the statistical combination of summary statistics from the various trials, but the term is sometimes also used to refer to the combination of the raw data. (*ICH E9*)

MIL-STD-105E: Any pharmaceutical system should have a quality control plan in place which describes the sampling procedure to be used in cases such as the one given in the example below. This annex shows how to use a quality control sampling system such as MIL-STD- 105D or E2. This USA military standard has been used for many years as a sampling procedure. Other similar systems are also described by ANSI and ISO.

Example:

A batch of Hepatitis B Vaccine is held at the central store. The temperature records show that the vaccine may have been exposed to freezing temperature during storage. The batch consists of 15,000 vials. It is impossible to do the shake test on all the vials and a representative sample must therefore be tested. How many vials should be tested in order to indicate the status of the batch?

Notes on sampling:

- 1. It is assumed that a “normal” inspection level will be adequate.
- 2. For freeze sensitive vaccines, freezing is a critical defect and therefore the acceptance/rejection criteria will always be 0 and 1. This means that you can accept the shipment if zero vials in the sample fail the test, but you **must** reject the shipment if one or more vials in the sample fails.

Step 1: Refer to below Table of the Standard. Find the appropriate size range for the shipment in the Lot or batch size column as shown in the example below.

Step 2: Find the matching sample size code in the General Inspection Levels column II as shown in the example.

Sample size code letters, MIL-STD-105E

Lot or batch size			Special inspection levels				General inspection levels		
			S-1	S-2	S-3	S-4	I	II	III
2	to	8	A	A	A	A	A	A	B
9	to	16	A	A	A	A	A	B	C
16	to	25	A	A	B	B	B	C	D
26	to	50	A	B	B	C	C	D	E
51	to	90	B	B	C	C	C	E	F
91	to	150	B	B	C	D	D	F	G
151	to	280	B	C	D	E	E	G	H
281	to	500	B	C	D	E	F	H	J
501	to	1,200	C	C	E	F	G	J	K
1,201	to	3,200	C	D	E	G	H	K	L
3,201	to	10,000	C	D	F	G	J	L	M
10,001	to	35,000	C	D	F	H	K	M	N
35,001	to	150,000	D	E	G	J	L	N	P
150,001	to	500,000	D	E	G	J	M	P	Q
500,001	to	over	D	E	H	K	N	Q	R

↑

Step 1:
Shipment size

↑

Step 2:
“Normal” inspection level needed
A shipment of 15,000 vials requires
inspection level **M**

Step 3: Use the below Table of the Standard to determine sample size and acceptance/rejection criteria.

Single sampling plans for normal inspection (master table)

Sample code letter	Sample size Size	Acceptable quality levels (normal inspection)																				65	100	150	250	400	650	1000	
		0.010	0.015	0.025	0.040	0.065	1.0	1.5	2.5	4.0	6.5	10	15	25	40	65	100	150	250	400									
A	2	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
B	3	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
C	5	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
D	8	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
E	13	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
F	20	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
G	32	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
H	50	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
J	80	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
K	125	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
L	200	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
M	315	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
N	500	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
P	800	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
Q	1,250	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
R	2,000	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re

Use first sampling plan below arrow, if sample size equals or exceeds lot or batch size, do 100% inspection.
Use first sampling plan above arrow
Ac Acceptance number
Re Rejection number

In this example, a randomly selected sample of 315 vials must be tested and zero vials are allowed to fail the test for acceptance

Acceptance and Rejection criteria

Sample Size

Min/max: Assigned minimum and maximum stock levels designed to ensure that a programme does not run out of supplies and also does not become overstocked. (WHO)

Minimum payload: The amount of product intended to be shipped with the least amount of thermal mass. (WHO)

Minimum rated ambient temperature: The lowest constant ambient at which a WHO prequalified vaccine refrigerator (with full vaccine load) can maintain the vaccine storage compartment within the acceptable temperature range. This is established by challenging the appliance by reducing the ambient temperature in 5°C increments below the lower limit for the model's rated temperature zone, down to a minimum of -10°C. Once established, this figure is displayed in the blue sector of the temperature zone symbol (WHO). See *acceptable temperature range (for refrigerators)* and *temperature zone symbols for refrigerators*.

Minimum stock level: The least amount of stock that programmes should have in stock or the level which, when reached, initiates a reorder; usually expressed as the number of months of supply. It is the amount of stock used between placing and receiving an order plus the safety stock. Also known as "reorder level" and "request indicator". (WHO)



Solar direct drive refrigerator is a typical example of mixed system use (Military Systems Technology)

Minor AEFI: An event that is not "serious" and that has no potential risk to the health of the recipient of the vaccine. (WHO)

Mixed systems: Mixed systems use both active and passive cooling technology, such as a solar direct drive. This kind of mixed system works actively when there is sun, and relies on the ice produced when there is not enough insolation. (WHO)

Model Formulary (WHO): A source of independent information on essential medicines for pharmaceutical policy-makers and prescribers worldwide, published by the WHO. For each medicine the Formulary provides information on use, dosage, adverse effects, contraindications and warnings, supplemented by guidance on selecting the right medicine for a range of conditions. WHO publishes model formularies for adults and children separately. (WHO)

Model List of Essential Medicines: WHO Model List of Essential Medicines serves as a guide for the development of national and institutional essential medicine lists, and is updated and revised in every two years by the WHO Expert Committee on Selection

and Use of Medicines. The first list was published in 1977 and the latest version is the 19th (April 2015). WHO also publishes a separate model list for essential medicines for children up to 12 years of age. The 5th edition of the Model List of Essential medicines for Children was published in April 2015.

Both documents list essential medicines in core and complementary lists. The “core list” presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment. The “complementary list” presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings. (WHO)

Monitor: A person appointed by, and responsible to, the sponsor or CRO for the monitoring and reporting of progress of the trial and for verification of data. (WHO)

Months of supply: An indication of current stock levels’ lasting based on the average monthly consumption (or issue data). This can easily be calculated by dividing the amount of a certain product on stock by average monthly consumption.

$$\text{Months of supply} = \frac{\text{Quantity in hand}}{\text{Average monthly consumption}}$$

Montreal Protocol: The Montreal Protocol on Substances that Deplete the Ozone Layer was designed to reduce the production and consumption of ozone depleting substances in order to reduce their abundance in the atmosphere, and thereby protect the earth’s fragile ozone layer. The original Montreal Protocol was agreed on 16 September 1987 and entered into force on 1 January 1989. The Montreal Protocol includes a unique adjustment provision that enables the Parties to the Protocol to respond quickly to new scientific information and agree to accelerate the reductions required on chemicals already covered by the Protocol. These adjustments are then automatically applicable to all countries that ratified the Protocol. Since its initial adoption, the Montreal Protocol has been adjusted eight times. For the full text visit <http://goo.gl/zeaHm>



Postal Corporation of Kenya issued three stamps to mark the 40th anniversary of the United Nations Environment Programme (UNEP), one on Montreal Protocol (June 2012)

Multi dose vial policy (MDVP): A WHO policy on using multi dose vials explaining which ones can be safely used for subsequent immunization sessions and which ones should be discarded at the end of the session.

All opened WHO-prequalified multi-dose vials of vaccines should be discarded at the end of the immunization session, or within six hours of opening, whichever comes first, UNLESS the vaccine meets all four of the criteria listed below. If the vaccine meets the four criteria, the opened vial can be kept and used for up to 28 days after opening. The criteria are as follows.

1. The vaccine is currently prequalified by WHO.
2. The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO. (*Consult each individual vaccine product sheet at the WHO prequalification website, referencing the description "Handling of opened multi-dose vials" <http://goo.gl/lt1Wqv>*)
3. The expiry date of the vaccine has not passed.
4. The vaccine vial has been, and will continue to be, stored at WHO- or manufacturer recommended temperatures; furthermore, the vaccine vial monitor, if one is attached, is visible on the vaccine label and is not past its discard point, and the vaccine has not been damaged by freezing.

For vaccines that are not prequalified by WHO, independent determinations on preservative efficacy, sterility, presentation and stability may not have been made by a functional national regulatory authority. Consequently, this could mean that the vaccine does not meet the WHO requirements on safety and efficacy, which form the minimum recommended standard for keeping multi-dose vaccine vials opened for more than six hours. Therefore, WHO recommends using non WHO-prequalified vaccines as soon as possible after opening, and respecting the time limit for using opened vials as indicated by the manufacturer's instructions in the package insert. If this information is not indicated in the package insert, WHO recommends discarding all non WHO-prequalified vaccine products within six hours after opening or at the end of the immunization session, whichever comes first. This policy statement further outlines conditions under which the MDVP can be implemented safely, including, but not limited to, adherence to good immunization practices.

Multicentre trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator. (*ICH E9*)

Multisource (generic) pharmaceutical product: Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable. (*WHO*)

N

National control laboratory (NCL): In countries where biological products are produced, the NRA should have appropriate expertise to evaluate the adequacy of the manufacturer’s establishment and facilities, starting materials, production processes, control-tests procedures and product specifications, to determine whether they meet international and/or national standards/requirements. These control activities should be fully independent of those of the manufacturer; ideally the national laboratory facilities should form a single administrative unit designated as the national control laboratory. The NCL may be administered directly by, or on behalf of, the NRA. (WHO)

National regulatory authority (NRA): Government agencies tasked with regulating and supervising pharmaceuticals and biological products such as vaccines released for public distribution. All countries need some sort of NRA, but “producing” countries need to exercise six critical control functions in a competent and independent manner backed up with enforcement power. “Procuring” countries also need minimum four of these six critical functions while “donor dependent” recipient countries need two. (WHO)

Critical control functions of NRAs depending on the vaccine source (WHO)

Vaccine source	Licensing	Post marketing surveillance	Lot release	Laboratory access	GMP inspections	Clinical evaluation
Donor dependent/UN agency						
Procuring						
Producing						

Required functions are indicated by shading

Negative likelihood ratio: Proportion of probability of individual with the condition having a negative test to probability that an individual without disease has a negative test. Since numerator is the converse of sensitivity, and the denominator is the specificity, it can also be explain as proportion of converse of sensitivity to specificity. Also see *validity*.

Negative predictive value: The probability that subjects with a negative diagnostic test truly do not have the positive condition (disease). Also see *validity*.

Net storage capacity: The total volume available for storing TTSPPs, taking account of the type of load support system employed (floor-standing pallets, adjustable pallet racking, shelving units or cabinet). Net storage capacity is calculated by multiplying the gross storage capacity of the load support system by the utilization factor (less than one) that can be achieved for the chosen stock-keeping unit type. (*WHO*)

Non-Article 5 country: Parties to the Montreal Protocol that have an ODS consumption of greater than 0.3 kg per capita on the date of entry of the Montreal Protocol, or at any time thereafter within 10 years of the date of entry into force of the Protocol.

Montreal Protocol: Non-Article 5 countries (UNEP Ozone Secretariat)

1.	Andorra	26.	Latvia
2.	Australia	27.	Liechtenstein
3.	Austria	28.	Lithuania
4.	Azerbaijan	29.	Luxembourg
5.	Belarus	30.	Malta
6.	Belgium	31.	Monaco
7.	Bulgaria	32.	Netherlands
8.	Canada	33.	New Zealand
9.	Cyprus	34.	Norway
10.	Czech Republic	35.	Poland
11.	Denmark	36.	Portugal
12.	Estonia	37.	Russian Federation
13.	European Union	38.	Romania
14.	Finland	39.	San Marino
15.	France	40.	Slovakia
16.	Germany	41.	Slovenia
17.	Greece	42.	Spain
18.	Holy See	43.	Sweden

19.	Hungary	44.	Switzerland
20.	Iceland	45.	Tajikistan
21.	Ireland	46.	Ukraine
22.	Israel	47.	United Kingdom
23.	Italy	48.	United States of America
24.	Japan	49.	Uzbekistan
25.	Kazakhstan		

Under the amendments and adjustments to the Protocol, non-Article 5 parties were required to phase out production and consumption of: halons by 1994; chloro-fluorocarbons (CFCs), carbon tetrachloride, hydrobromochlorofluorocarbons and methyl chloroform by 1996; bromochloromethane by 2002; and methyl bromide by 2005. Article 5 parties were required to phase out production and consumption of hydrobromochlorofluorocarbons by 1996, bromochloromethane by 2002, and CFCs, halons and carbon tetrachloride by 2010. Article 5 parties must still phase out production and consumption of methyl chloroform and methyl bromide by 2015. Under the accelerated phase-out of hydrochlorofluorocarbons (HCFCs) adopted at the Nineteenth Meeting of the Parties to the Montreal Protocol (MOP 19), HCFC production and consumption by non-Article 5 parties was frozen in 2004 and is to be phased out by 2020, while for Article 5 parties, HCFC production and consumption was to be frozen by 2013 and phased out by 2030 (with interim targets prior to those dates, starting in 2015).

Non-clinical evaluation of vaccines: All in vivo and in vitro testing performed before and during clinical development of vaccines. The potential toxicity of a vaccine should be assessed not only prior to initiation of human trials, but throughout clinical development. (*WHO*)

Non-clinical study: Biomedical studies not performed on human subjects.

Non-inferiority trial: A trial with the primary objective of showing that the response to the investigational product is not clinically inferior to a comparative agent (active or placebo control). (*ICH E9*)

Non-maleficence: Doing no harm.

Numerator: The number of parts being considered, where each part is an equal fraction of the whole; dividend.



EPS boxes with nylon exterior (Sofrigam)

Nylon: Group of plastics known as polyamids. The majority of nylons tend to be semi-crystalline and are generally very tough materials with some thermal and good chemical resistance. Usually used in bags for short transport, such as from hospital/pharmacy to home. In other cases, nylon is used as exterior material for EPP, EPS and XPS type packaging.



Ongoing stability study: The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected re-test period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP. (*WHO*)

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g., changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains, and can be expected to remain, within specifications under the storage conditions indicated on the label, within the re-test period in all future batches.

After a marketing authorization has been granted, the stability of the FPP should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g., changes in levels of impurities or dissolution profile) associated with the formulation in the container closure system in which it is marketed. The purpose of the ongoing stability programme is to monitor the product over its shelf-life and to determine that the product remains, and can be expected to remain, within specifications under the storage conditions on the label.

Operational qualification (OQ): The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications. (*WHO*)

Out-of-specification: A material, product, or service failing to meet one or more of the applicable specifications.

Outbreak: An epidemic limited to localized increase in the incidence of a disease, e.g., in a village, town, or closed institution; upsurge is sometimes used as a euphemism for outbreak; the sudden increase in the incidence of a disease or condition in a specific area. (*WHO*)

P

Package insert: A document provided along with a prescription or over-the-counter medication to provide additional information about the drug product. It is also known as “prescribing information” in the United States; and “patient information leaflet” for human medicines and “package leaflet” for veterinary medicines in Europe. National regulatory agencies determine the requirements for package inserts. A typical package insert includes the following information:

- Brand name and generic name of the product.
- Clinical pharmacology - explaining how the medicine works, how it is absorbed and eliminated, and what its effects are likely to be at different concentrations. Under this section, various clinical trials (studies) results may be given and/or explanations of the medication’s effect on various populations (e.g. children, women, etc.).
- Indications and usage - uses (indications) for which the drug has been approved. Physicians legally can and often do prescribe medicines for purposes not listed in this section (so-called “off-label uses”).
- Contraindications - lists situations in which the medication should not be used.
- Warnings - covers possible serious side effects that may occur.
- Precautions - explains how to use the medication safely including physical impairments and drug interactions.
- Adverse reactions - lists all side effects observed in all studies of the drug.
- Drug abuse and dependence - provides information regarding whether prolonged use of the medication can cause physical dependence (if applicable)
- Overdosage - gives the results of an overdose and provides recommended action in such cases

- Dosage and administration - gives recommended dosage(s); may list more than one for different conditions or different patients (e.g., lower dosages for children)
- How supplied - explains in detail the physical characteristics of the medication including color, shape, markings, etc., and storage information.

WHO also issues requirements for its prequalified vaccine products. These package inserts come in several languages.

The very first patient package insert required by the USFDA was in 1968, mandating that isoproterenol inhalation medication must contain a short warning that excessive use could cause difficult breathing.

IPM 22085-2

Euforvac-Hib™ Inj.

Adsorbed Diphtheria-Tetanus-whole cell Pertussis-Hepatitis B (DNA)
and Haemophilus influenzae type b conjugate vaccine

DESCRIPTION The vaccine is composed of Hib vaccine as a freeze dried powder which is reconstituted using liquid DTaP-HepB vaccine, Euforvac™ Inj. as a diluent.

DTaP-HepB vaccine (liquid) The vaccine is a liquid containing purified diphtheria toxoid (DT), tetanus toxoid (TT), whole cell pertussis (wP) and recombinant hepatitis B surface antigen (HBsAg) as active ingredients, adsorbed on aluminum salts as an adjuvant and preserved with thimerosal. The diphtheria and tetanus toxins obtained from cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* are identified and purified. The pertussis bacteria is treated with heat and thimerosal to kill them and inactivate their toxins. Purified HBsAg is produced using DNA recombinant technology in yeast cells (*Saccharomyces Cerevisiae*).

Hib vaccine (powder) The vaccine is a monovalent PRP-T conjugated vaccine for the prevention of *Haemophilus influenzae* type b disease in infants. The vaccine contains the lyophilized active pharmaceutical ingredients, contains the inactivated tetanus toxoid covalently linked with PRP per one dose. It also contains lactose exceptant as a formulation stabilizer.

COMPOSITION

Statement of active substances:

After reconstitution, one dose (0.5ml) contains:	
Diphtheria toxoid	15 Lf
Tetanus toxoid	10 Lf
Inactivated whole cell <i>Bordetella pertussis</i> suspension	24 IU
Purified HBsAg	10 µg
Purified capsular polysaccharide (PRP) of Hib conjugated to the tetanus 20-40 µg (toxoid/PRP-T)	10 µg

List of excipients:

Aluminum Hydroxide	0.38 mg (Al ³⁺)
Thimerosal	0.004 w/v%
Formaldehyde	0.01 w/v%
Polyorbate (Tween 80)	5 µg
Lactose	10.00 mg

INDICATION AND USAGE Euforvac-Hib™ inj. is indicated for active primary immunization against diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b in infants from 6 weeks of age.

ADMINISTRATION ONLY THE DTaP-HepB VACCINE PROVIDED SHOULD BE USED TO RECONSTITUTE THE HIB VACCINE. The lyophilizate must be reconstituted by adding the entire content of the supplied container of diluent to the vaccine vial. The vaccine pellet should be completely dissolved in the diluent. Following reconstitution, the vaccine should be inspected visually for any foreign particulate matter prior to administration. If observed, the vaccine must be discarded.

A sterile needle and sterile syringe must be used for the reconstitution of the vaccine and for each injection.

The reconstituted vaccine should be used the same day (preferably immediately but by no means beyond six hours after reconstitution), and only then if the vial has been maintained between +2°C and +8°C and protected from sunlight. If not used immediately after reconstitution, the vaccine should be kept on cold box or refrigerator at +2°C to +8°C to maintain the temperature between +2°C to +8°C. Any opened container remaining at the end of a session (within six hours of reconstitution) should be discarded.

The liquid vaccine vial should be shaken before use to homogenize the suspension. The vaccine should be injected intramuscularly. The anterolateral aspect of the upper thigh is the preferred site of injection. An injection into a child's buttocks may cause injury to the sciatic nerve and is not recommended. It must not be injected into the skin as this may give rise to local reaction. One quadrant dose is 0.5ml.

IMMUNIZATION SCHEDULE Euforvac-Hib™ inj. should NOT be used for the birth dose. In countries where pertussis is of particular danger to young infants, the combination vaccine should be started as soon as possible with the first dose given as early as 6 weeks, and two subsequent doses given at 4-week intervals.

The Euforvac-Hib™ inj. can be given safely and effectively at the same times as BCG, measles, polio(OPV or IPV), and yellow fever vaccines and vitamin A supplementation. If Euforvac-Hib™ inj. is given at the same time as other vaccines, it should be administered at a separate site. It should not be mixed in the vial or syringe with any other vaccine.

SIDE EFFECTS The type and rate of severe adverse reactions do not differ significantly from the DTaP, HepB and Hib vaccine reactions described separately.

For DTaP, mild local or systemic reactions are common. Some temporary swelling, tenderness and redness at the site of injection together with fever occur in a large proportion of cases. Occasionally severe reactions of high fever, irritability and screaming develop within 24 hours of administration. Hypotonic-hyporeflexive episodes have been reported. Febrile convulsion have been reported at a rate of one per 12500 doses administered. Administration of acetaminophen at the time and 4-8 hours after immunization decreases the subsequent incidence of febrile reactions. The natural childhood encephalopathy study in the United Kingdom showed a small increased risk of acute encephalopathy (primarily seizures) following DTP immunization. However subsequent detailed reviews of all available studies by a number of groups, including the United States Institute of Medicine, the Advisory Committee on Immunization Practices, and the pediatric associations of Australia, Canada, the United Kingdom and the United States, concluded that the data did not demonstrate a causal relationship between DTaP and chronic nervous system dysfunction in children. Thus there is no scientific evidence that these reactions have any permanent consequences for the children. (In Weekly Epidemiological Record, No. 18, 7 May 1999, Page 139)

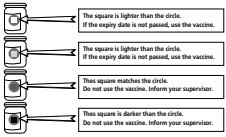
Hepatitis B vaccine is very well tolerated. In placebo-controlled studies, with the exception of local pain, reported events such as myalgia and transient fever have not been more frequent than in the placebo group. Reports of severe anaphylactic reactions are very rare. Available data do not indicate a causal association between hepatitis B vaccine and Guillain-Barre syndrome, or demyelinating disorders including multiple sclerosis, nor is there any epidemiological data to support a causal association between hepatitis B vaccination and chronic fatigue syndrome, arthritis, autoimmune disorders, autism, sudden infant death syndrome, or diabetes.

Hib vaccine is very well tolerated. Localized reactions may occur within 24 hours of vaccination, when recipients may experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required. Mild systemic reactions, including fever, rarely occur following administration of Hib vaccines. More serious reactions are very rare, a causal relationship between more serious reactions and the vaccine has not been established.

CONTRAINDICATIONS Known hypersensitivity to any component of the vaccine, or a severe reaction to a previous dose of the combination vaccine or any of its constituents is an absolute contraindication to subsequent doses of the combination vaccine or the specific vaccine known to have provoked an adverse reaction. There are few contraindications to the liquid dose of DTaP-Hib or abnormal cerebral signs in the newborn period or other serious neurological abnormality are contraindications to the pertussis component. In this case, the vaccine should not be given as a combination vaccine but DT should be given instead of DTaP and Hep B and Hib vaccine given separately. The vaccine will not harm individuals currently or previously infected with the hepatitis B virus.

Immune deficiency Individuals infected with the human immunodeficiency virus (HIV), both asymptomatic and symptomatic, should be immunized with combined vaccine according to standard schedules.

STORAGE The components of a combination vaccine must be stored in a refrigerator and transported between +2°C and +8°C. The Euforvac-Hib™ Inj. **COMPONENT MUST NOT BE FROZEN**. Do not use after the expiry date stated on the pack.



The square is lighter than the circle. If the expiry date is not passed, use the vaccine.

The square is lighter than the circle. If the expiry date is not passed, use the vaccine.

This square matches the circle. Do not use the vaccine. Inform your supervisor.

This square is darker than the circle. Do not use the vaccine. Inform your supervisor.

PRESENTATION The vaccine comes in single dose vials or vials of 2 doses.

HOW SUPPLIED 0.5ml./vial, cartons of 1 set of 2 vials: 5 sets of 2 vials
1.0ml./vial, cartons of 1 set of 2 vials: 5 sets of 2 vials

Issue date: January, 1, 2013

Manufactured by
LG Life Sciences

601, Yonge-dong, Inan-si, Jeonbuk-do, Korea
Branch of O.T.P. Inc. (an indirect subsidiary of LG Life Sciences)
Daejeon • Yuseong-Gu, No. 32, Yuseong-Ro, Daejeon

An example of a package insert in English (DTwP-HepB+Hib vaccine from LG Life Sciences Ltd. A WHO prequalified vaccine)

Packaging: Technology of enclosing or protecting products for distribution, storage, sale and use.

Packing slip: Transaction record sent with products that lists the names and quantities of each product shipped. Packing slip is usually paired with a receiving record. (WHO)

Packout: An assembled package that includes the product to be shipped (alternatively, simulated product in its primary packaging form used for its commercial presentation, the insulated shipper or container, any and all necessary auxiliary and/or associated components and ancillary packaging components such as temperature stabilizing medium, secondary packaging, partitions, bubble wrap, data loggers or other temperature monitoring units, and dunnage. (WHO)



Wooden and plastic pallets
(Andrea Crisante and nacykoa43, Shutterstock)

Pallet: Wooden or plastic platform designed to be lifted by pallet jack or forklift truck. Typically used for storing and handling tertiary cartons. Since pallets form an important part in the maritime industry, several norms and measures have been established by the ISO (International Organization for Standardization). Through such norms, it has been sought to bring the entirety of the freight operations which palletize their cargo consignments under a wider and common spectrum. The normative standardisation for pallets has been regulated in their sizing. Pallet sizes matter hugely while loading on palletized cargo ships as depending on the nature of the cargo, the optimal sized pallet is utilised to support the cargo consignments. See also *ISO pallets* and *EUR pallet*.

Pallet shipper: A combination of different products stacked together and shrink-wrapped on a pallet for shipment to a retailer. As for pharmaceuticals, it provides bulk holding of pharmaceutical products either in a single or multiple payload cavities with the advantage of increasing the payload thus reducing shipping cost.



RePak96™ 96hr insulated pallet shipper with two independent payload cavities
(Cryopak)

Pandemic: An epidemic occurring over a very wide area, crossing international boundaries and usually affecting a large number of people. (WHO)

Passive cooling: See *passive systems*.

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others. (WHO)

Performance qualification (PQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications. (WHO)

Performance, Quality and Safety (PQS): A WHO project to establish performance specifications, test procedures and prequalify a comprehensive range of immunization equipment, injection devices and other products needed for safe and effective immunization delivery.

The PQS on-line catalogue includes details of all immunization-related products currently pre-qualified by WHO for procurement by United Nations agencies. The catalogue replaces the old WHO/UNICEF Product Information Sheets (PIS), the last edition of which was published in 2000. Only products included in the PQS catalogue are now recommended to be purchased by UN agencies. The catalogue and the individual product data sheets are available on the internet only at: <http://goo.gl/q2N0op>

There is no hardcopy version. Each edition of the catalogue is date-stamped. It is updated regularly to ensure that the information it contains is current.

Product categorization for PQS prequalification scheme (WHO)

- E001 : Cold rooms, freezer rooms and related equipment;
- E002 : Transport (guideline only);
- E003 : Refrigerators and freezers;
- E004 : Insulated containers;
- E005 : Ice-packs, cool-packs and warm-packs;
- E006 : Temperature monitoring devices;
- E007 : Cold chain accessories;
- E008 : Single-use injection devices;
- E009 : (not currently used);
- E010 : Waste management equipment;
- E011 : Specimen collection equipment;
- E012 : (not currently used);
- E013 : Therapeutic injection devices.

Following initial pre-qualification, all listed products must pass an annual review. This process takes account of feedback from purchasing agencies and users. Adverse reports may lead to product modifications, to suspension; or, in serious cases, to removal from the catalogue.

Perishable Cargo Regulations (PCR): A worldwide standard and an essential reference guide endorsed by IATA Live Animals and Perishables Board (LAPB) for all parties involved in the packaging and handling of temperature sensitive products from the health care and food sectors, including pharmaceutical products and non-hazardous biological materials. The PCR includes:

- Up-to-date airline and government requirements pertaining to the transport of perishable cargo
- Requirements on handling, marking & labelling
- Necessary packaging requirements
- Information on the necessary documentation required when transporting perishable cargo
- A comprehensive classification of 100's of perishable commodities

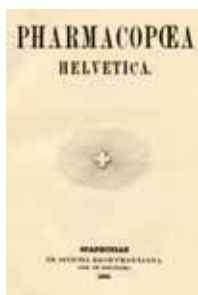
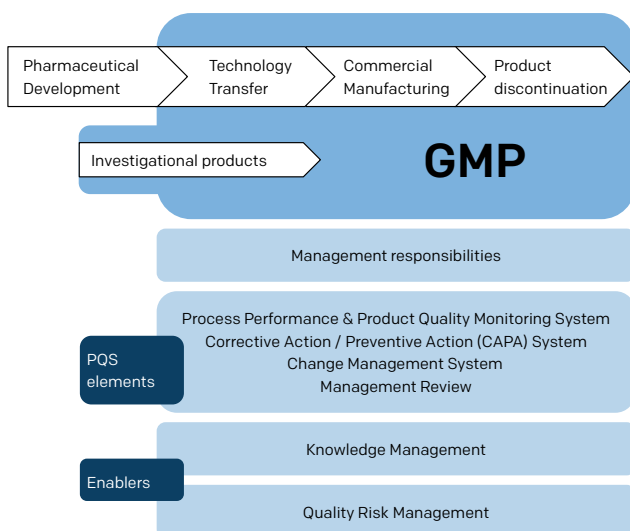
Perishables: Liable to perish, especially naturally subject to quick deterioration or decay by time or exposition to adverse temperature and humidity (*IATA*). Perishable goods (such as fruits, flowers and vegetables) were among the first commodities carried by air.

Pharmaceutical equivalents: Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standards; and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance. (*WHO*)

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included. (*WHO*)

Pharmaceutical Quality System (PQS): Management system to direct and control a pharmaceutical company with regard to quality. (*ICH Q10 based upon ISO 9000:2005 – revised by ISO 9000:2015*)

Pharmaceutical Quality System Model (ICH Q10)



The first “Pharmacopoeia Helvetica” accomplished by the private initiative of the young Swiss Pharmacists Association (1865) and the latest one published by Swissmedic (2013)



Pharmacopoeia: A reference work for pharmaceutical drug specifications, a book containing directions for the identification of compound medicines, and published by the authority of a government or a medical or pharmaceutical society.

Pharmacopoeial text: The pharmacopoeial monographs, general test chapters, and analytical methods emanating from the three regional pharmacopoeias. (*ICH Q4B*)

Pharmacovigilance (vaccine): The science and activities relating to the detection, assessment, understanding, prevention and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues (*CIOMS*).

The goal of vaccine pharmacovigilance is the early detection of and appropriate and timely response to adverse events following immunization in order to minimize negative effects to the health of individuals and lessen the potential negative impact on immunization of the population. Continuous risk-benefit assessment and risk management are integral to the vaccine pharmacovigilance process.

There is a very high level of safety required for vaccines. Elements to consider when conducting vaccine pharmacovigilance include the following (*CIOMS*):

- Vaccines are usually administered to healthy people, including infants.
- Vaccines may be administered to the vast majority of the population or of a birth cohort or to groups at high risk for disease complications.
- Subpopulations may be more susceptible to experience certain adverse events following immunization.
- The age at the time of immunization may coincide with the emergence of certain age-related diseases (e.g., neurodevelopmental disorders).
- Immunization with certain vaccines is mandated in some countries.
- The benefits of immunization may not be immediately visible, particularly if the target disease incidence is low.
- Due to the low acceptance of risks, intensive investigation of serious adverse events following immunization, even if rare, is necessary.
- Non-serious adverse events following immunization also should be carefully monitored because they may signal a potentially larger problem with the vaccine or immunization, or have an impact on the acceptability of immunization in general.
- Appropriate methods are needed to detect and assess any potential causal association of serious, rare, and/or delayed adverse events, or of adverse events in subgroups, with immunization.
- Consideration of dechallenge and rechallenge differs for vaccines compared with other medicinal products. Vaccines are frequently administered only once or with long intervals, and serious adverse events following immunization often prevent further vaccine administration. Dechallenge may not be applicable to vaccines, given their long-term immunological effects, and rechallenge information is only rarely available.
- Vaccines are often administered concomitantly with other vaccines, making causal attribution to a specific vaccine difficult.
- The administration of live vaccines can lead to disease caused by the attenuated organisms in vaccinees or their contacts; this should be differentiated from coinciding natural infection.
- Vaccines are complex biological products, which may include multiple antigens, live organisms, adjuvants, and preservatives. Each component may have unique safety implications. Variability and (even small) changes in the manufacturing process may have impact on quality, protective effect, and safety. Batch information is of crucial importance.

- New vaccines are increasingly based on new production and administration technologies, with new adjuvants and alternative routes of administration, necessitating adapted safety monitoring systems.
- Depending on the mode and extent of use of a vaccine, it may elicit a degree of herd immunity to a specific disease. When assessing the risk-benefit of a vaccine, herd immunity effects as well as individual protection need to be taken into account.
- Effective communication regarding the safety of vaccines and immunization is challenging. Despite strong evidence that a serious adverse event is not related to immunization, perceptions of harm may persist and may potentially have a negative impact on immunization of the population.

Physical inventory: A count of all the commodities on stock to verify that the amount that is actually stored is the same as the quantity listed in the stock-keeping records. Operations are usually shut-down during a physical inventory. Sometimes errors occur in counting the quantities of commodities entering or leaving a store. A regular physical check is the only way to ensure that stock records and running balances are accurate, matching and complete. If the result of counting a stock item is different from that shown in the record, the stock should be counted again to ensure there was no counting error. If a second count gives the same result as the first, the stock record is probably in error, and must be corrected. (*WHO*)

The following actions should be taken:

- If more items are counted than are recorded: Record the additional amount in the loss/adjustment column of batch and inventory control cards with an explanation of the reason in the remarks column.
- If fewer items are counted than are recorded: Record the missing amount as a negative value in the loss/adjustment column of batch and inventory control cards with an explanation of the reason in the remarks column. In addition a loss report should be filled (see *loss report*).

Corrected balances should be entered on a separate line in all related cards such as batch card, inventory stock card, and/or stock ledger, below the old balance, and a note should be written with responsible staff signature beside it, to indicate that a physical check has confirmed the new balance. This corrected total should be used for all future stock calculations.

Sample physical inventory report for a vaccine storage facility (WHO)

Name of the store:							
Report number:							
Vaccine / diluent		Batch number	Expiry date	Current stock	Freeze indicator status	VVM status	Remarks
OPV	1						
	2						
	3						
Total							
DTP+HepB	1						
	2						
	3						
Total							
BCG	1						
	2						
	3						
Total							
BCG diluent	1						
	2						
	3						
Total							
Measles	1						
	2						
	3						
Total							
Measles diluent	1						
	2						
	3						
Total							
Reconstitution syringe	1						
	2						
	3						
Total							
AD syringe BCG	1						
	2						
	3						
Total							
AD syringe 0.5 ml	1						
	2						
	3						
Total							
Safety box	1						
	2						
	3						
Total							
Inventory done by	Title			Date		Signature	
Approved by	Title			Date		Signature	

PIC/S: The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP.

PIC/S' mission is "to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products". This is to be achieved by developing and promoting harmonized GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organizations.

There are currently 46 Participating Authorities in PIC/S (Convention and Scheme taken together).

Participating authorities in PIC/S

<ul style="list-style-type: none"> ■ ANMAT, Argentinean National Institute of Drugs ■ TGA, Australian Therapeutic Good Administration ■ AGES, Austrian Medicines and Medical Devices Agency ■ AFMPS, Belgian Federal Agency for Medicines and Health Products ■ HPFBI, Canadian Health Products and Food Branch Inspectorate ■ TFDA, Taiwan Food and Drug Administration ■ CyPHS, Cypriot Pharmaceutical Services ■ SÚKL, Czech State Institute for Drug Control ■ ISCVBM, Czech Institute for State Control of Veterinary Biologicals and Medicines ■ DHMA, Danish Health and Medicines Authority ■ SAM, Estonian State Agency of Medicines ■ FIMEA, Finnish Medicines Agency ■ ANSM, French National Agency for Medicines and Health Products Safety ■ ANSES, French Agency for Food, Environmental & Occupational Health Safety ■ BMG, German Federal Ministry of Health ■ ZLG, Central Authority of the Laender for Health Protection regarding Medicinal Products and Medical Devices ■ EOF, Greek National Organization for Medicines ■ NIPN, Hungarian National Institute of Pharmacy and Nutrition ■ IMA, Icelandic Medicines Agency ■ NADFC, Indonesian National Agency for Drug and Food Control 	<ul style="list-style-type: none"> ■ HPRA, Health Products Regulatory Authority ■ ISCP, Israeli Institute for Standardization and Control of Pharmaceuticals ■ AIFA, Italian Medicines Agency ■ MHLW, Japanese Ministry of Health, Labour and Welfare ■ PMDA, Japanese Pharmaceuticals and Medical Devices Agency ■ MFDS, Korea (Republic of) Ministry of Food and Drug Safety ■ ZVA, Latvian State Agency of Medicine ■ AG, Liechtenstein's Office of Healthcare ■ SMCA, Lithuanian State Medicines Control Agency ■ NPCB, Malaysian National Pharmaceutical Control Bureau ■ MAM, Maltese Medicines Authority ■ IGZ, Dutch Health Care Inspectorate ■ Medsafe, New Zealand's Medicines and Medical Devices Safety Authority ■ NOMA, Norwegian Medicines Agency ■ MPI, Polish Main Pharmaceutical Inspectorate ■ INFARMED IP, Portuguese National Authority of Medicines and Health Products, IP ■ NAMMD, Romanian National Agency for Medicines and Medical Devices ■ HSA, Singapore's Health Sciences Authority ■ SIDC, Slovak State Institute for Drug Control ■ JAZMP, Slovenian Agency for Medicinal Products and Medical Devices ■ MCC, South African Medicines Control Council ■ AEMPS, Spanish Agency of Medicines and Medical Devices
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The PIC (Pharmaceutical Inspection Convention) was founded in October '70 by the European Free Trade Association (EFTA), under the title of "The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products". The initial members comprised the 10 member countries of EFTA at that time. In the early 1990s it was realized that because of an incompatibility between the Convention and European law, it was not possible for new countries to be admitted as members of PIC. European law did not permit individual EU countries that were members of PIC to sign agreements with other countries seeking to join PIC. As a consequence the Pharmaceutical Inspection Co-operation Scheme was formed on 2 November 1995. The Pharmaceutical Inspection Co-operation Scheme is an informal agreement between health authorities instead of a formal treaty between countries. PIC and the PIC Scheme, which operate together in parallel, are jointly referred to as PIC/S. PIC/S became operational in November 1995.

Pictogram: A graphical composition that may include a symbol and other graphical elements, such as a border, background pattern or color that is intended to convey specific information.

Pilot-scale batch: A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger; unless otherwise adequately justified. (WHO)

PIR (Polyisocyanurate): A thermoset plastic typically produced as a foam and used as rigid thermal insulation. PIR is typically produced as a foam and used as rigid thermal insulation mainly in palletized shippers.



**BulkPak PIR series
insulated shipper (Cryopak)**

Placebo control: A comparator in a vaccine trial that does not include the antigen under study. In studies of monovalent vaccines this may be an inert placebo (e.g., saline solution or the vehicle of the vaccine), or an antigenically different vaccine. In combined vaccines, this may be a control arm in which the component of the vaccine being studied is lacking. (WHO)

Positive likelihood ratio: Proportion of probability of individual with the condition having a positive test to probability that an individual without disease has a positive test. Since numerator is the definition of sensitivity, and the denominator is the con-

verse of specificity, it can also be explain as proportion of sensitivity to converse of specificity. Also see *validity*.

Positive predictive value: The probability that subjects with a positive diagnostic test truly have the positive condition (disease). Also see *validity*.

Post-marketing surveillance: A system for monitoring adverse events following licensure (WHO). Post-marketing surveillance can be passive or active and its objectives include, but are not limited to, the following:

- the identification of rare adverse reactions not detected during pre-licensure studies; and
- the identification of risk factors or pre-existing conditions that may promote reactions.

Potency: The measure of biological activity, using a suitable quantitative biological assay, based on the attribute of the product that is linked to the relevant biological properties. (WHO)

Pre-clinical evaluation of vaccine: All in vivo and in vitro testing carried out prior to the first testing of vaccines in humans. This is a prerequisite to the initiation of clinical trials and includes product characterization, proof of concept/immunogenicity studies and animal safety testing. (WHO)

Pre-clinical toxicity study: A study designed with the primary purpose of demonstrating the safety and tolerability of a candidate vaccine product. The design of the pre-clinical toxicity study should meet the criteria outlined in the section on study design to be considered supportive of the intended clinical trial. (WHO)

Pre-exposure trial: A prospective trial in a population expected to be exposed to the pathogen under study within a predefined, relatively short, period. (WHO)

Precautionary pictograms: Pictograms indicating a recommended measure that should be taken to minimize or prevent adverse effects resulting from exposure to hazardous materials. They are always in blue background color and round shape.



Safety helmet
must be worn



Ear protection
must be worn



Safety harness
must be worn



Eye protection
must be worn



Respiratory equipment
must be worn



Face protection
must be worn



Safety overalls
must be worn



Safety boots
must be worn



Safety gloves
must be worn



Pedestrian must
use this route



General mandatory sign
(To be accompanied where
necessary by another sign)

Examples of (mandatory) precautionary pictograms (European Union)

Precautionary statement: A phrase (and/or pictogram) that describes recommended measures that should be taken to minimize or prevent adverse effects resulting from exposure to a hazardous product, or improper storage or handling of a hazardous product. (UN)

Precipitation coefficient: A multiplicative factor in explaining how many times faster the freeze damaged aluminum adjuvanted vaccine sediments compared to its non-frozen equivalent. Precipitation coefficient in WHO prequalified aluminum adjuvanted vaccines varies between 2 and 15. See also *sedimentation rate* and *shake test*.

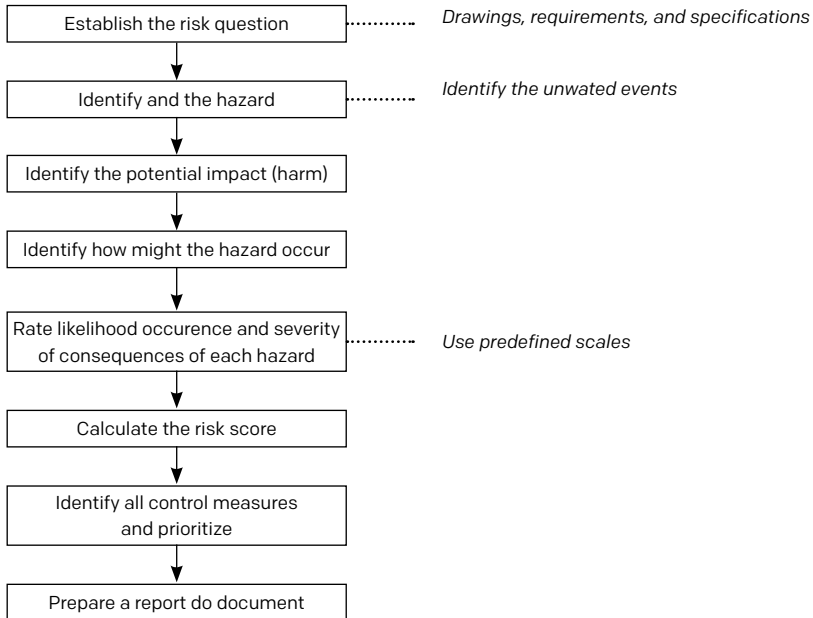
Precision: The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility. Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements. (ICH Q2/R1)

Preliminary Hazard Analysis (PHA): A tool that is used to determine if a particular, potential agent could be a hazard – a source of harm to something of value such as the defined critical quality attributes of a product (*J Vesper*). Also see *preliminary risk analysis (PRA)*.

Preliminary Risk Analysis (PRA): A qualitative, inductive, loosely structured tool that can be used to identify, consider, and reduce risks early in a new or changed process. A PRA can be done at early stages of conceptual design of a product or process. Because it is relatively easy to conduct and quite unstructured, it is the recommended first step in trying to assess risks in a new product or process. Results from a PRA may lead to the use of more extensive and specific risk assessment tools for more detailed analysis. The most common approach in PRA is to study existing hazards and then examine how the hazards could be expressed, what the impact would be and the probability if occurs. On the contrary to FMEA/FMECA, detectability of the hazard is not taken into account in typical PRA/PHA.

The very first step in PRA/PHA is to establish a “risk question” that is to be studied, e.g., “What are the associated risks in using refrigerators that are equipped with non-recording temperature monitoring systems and with local alarms at the service level?” For each risk question, a separate PRA/PHA should be conducted. Under each risk question, the unwanted event is defined by asking a simple question “what could happen?” Next step is to identify the harm (consequences) and potential causes of the hazardous situation. Each hazard then is rated based on a predefined scale for its likelihood of occurrence and the severity of consequence. Multiplication of these two factors gives the “risk score” or “risk index”. Once it is completed, all possible control measures to detect, prevent, and control the hazards.

PRA/PHA process (Kartoglu)



A typical PRA worksheet

Risk ID#	Hazard/ unwanted event	Harm/con- sequences	Potential causes	Likelihood of occur- rence (L)	Severity of conse- quence (S)	Risk score	Possible controls/ actions
Assign each entry a unique tracking number	What could happen?	What might be the poten- tial im- pact?	How might the hazard occur?	What is the likelihood that the hazard and harm will occur (rating scale)	How signif- icant is the impact (rating scale)	(Calculat- ed) L x S	What might help to detect, prevent and control the haz- ardous sit- uation?

Prequalified shipping container system: A packaging container or packaging system in which a DQ and OQ have already been established and documented by the manufacturer and the user has acquired sufficient documentation to meet their user requirement specification (URS).

Prevalence: The number of persons who have a particular disease at a specific time. (WHO)

Preventive action: Action to eliminate the cause of a potential nonconformity or other undesirable potential situation. Preventive action is taken to prevent occurrence.

Primary batch: A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf-life, as the case may be. A primary batch of an API should be at least a pilot-scale batch. For an FPP, two of the three batches should be at least pilot-scale batches, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Primary container: Bag, blister pack, strip, bottle, cartridge, vial, ampoule, prefilled device, plastic dispenser, tube, single dose container or the like containing tablet(s), capsule(s), liquid preparation or the like.

Primary vaccination: First vaccination, or series of vaccinations given within a pre-defined period, with an interval of less than six months between doses, to induce clinical protection. (WHO)

Primary vaccine store: A principal or main store that receives vaccine from the supplier.

Process failure: The manner in which a process fails to meet its intended purpose.

Process Performance and Product Quality Monitoring System: A system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement. As defined by the ICH Q10, the process performance and product quality monitoring system should:

1. Use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. The control strategy should facilitate timely feedback / feedforward and appropriate corrective action and preventive action;
2. Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);
3. Analyze parameters and attributes identified in the control strategy to verify continued operation within a state of control;
4. Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation;
5. Include feedback on product quality from both internal and external sources, e.g., complaints, product rejections, non-conformances, recalls, deviations, audits and regulatory inspections and findings;
6. Provide knowledge to enhance process understanding, enrich the design space (where established), and enable innovative approaches to process validation.

Application of process performance and product quality monitoring system throughout the product lifecycle (ICH Q10)

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

Process validation: Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a drug substance or intermediate meeting its predetermined specifications and quality attributes (*ICH Q7*). Process validation can include the collection and evaluation of data, from the process design stage throughout production, that establish scientific evidence that a process is capable of consistently delivering a quality drug substance. As an alternative to the traditional process validation, continuous process verification (*ICH Q8*) can be utilised in process validation protocols for the initial commercial production and also for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle.

Product characterization: A full battery of physical, chemical and biological tests conducted for a particular product. These tests include, but are not limited to, in-process control testing, testing for adventitious agents, testing process additives and process intermediates, and lot release. (*WHO*)

Product realization: Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorisation) and internal customers' requirements.

Product summary file: The product summary file contains general information on the company and its personnel, premises and equipment, copies of the national or regional licenses as appropriate, information on the composition of the vaccine, presentations offered, immunization schedules recommended, production methods, quality control procedures, specifications of intermediate and final products, and data on the stability, shelf-life, clinical efficacy and safety of the vaccine. For initial product assessments, a product summary file should be submitted for each vaccine to be assessed. For combination vaccines, information should be submitted on each of the component vaccines and on the combination itself.

Production batch: A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

Prohibitory signs: Signs prohibiting behavior likely to incur or cause danger. They are always round shape with black pictogram on white background, red edging and diagonal line.



Examples of prohibitory signs (EU)

Proportional rate: The number of cases of a particular condition as a proportion of the total number of cases of all conditions.

Protection at birth (PAB) indicator: The TT2+ indicator works well when coverage with TT is relatively low. However, as TT coverage increases, fewer women will need to receive TT (they are already protected) so the numerator will go down, but the denominator (births) will not. This will lead to an incorrect estimate of programme performance. One way to avoid this problem is by using the protection at birth indicator. This indicator measures the percentage of infants who were protected from NT at birth by the immunization of their mothers with TT before the birth.

$$\text{Percentage of protection at birth} = \frac{\text{Number of infants whose mothers had protective doses of TT}}{\text{Infants under 1 year of age or live births}} \times 100$$

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. (ICH E6/R1)

Protocol amendment: A written description of a change(s) to or formal clarification of a protocol. (ICH E6/R1)

Provisional shelf-life: A provisional expiry date which is based on acceptable accelerated and available long-term data for the FPP to be marketed in the proposed container closure system.

Public private partnership: A partnership between the public sector and the private sector for the purpose of delivering a project or a service traditionally provided by the public sector (EU). Some so-called public-private partnerships could be more accurately described as public sector programmes with private sector participation (WHO). Some examples of public private partnerships for health include Roll Back Malaria, Safe Injection Global Network, and Stop TB (all of which have secretariats in WHO).



In 2013, football legend and United Nations Development Programme (UNDP) Goodwill Ambassador Didier Drogba joined the United Against Malaria, a campaign of “Roll Back Malaria” partnership

Pull system: A distribution system in which the personnel who receive the supplies determine the quantities to order. In the pull systems however, the lower level facilities are responsible for ordering supplies. Decisions on quantity of shipments are made by lower level managers or by the functionary responsible for supply. A pull system is best when; there is no supply shortage, the responsibility for programme operations is decentralized, and lower levels have sufficient management and data processing skills. Also called as “requisition” system. (WHO)

PUR: Polyurethane – A polymer composed of a chain of organic units joined by carbamate (urethane) links. A two-component mixture composed of isocyanate and polyol resin comes together at the tip of a gun, and forms an expanding foam that is injected into a mold. PUR resistance to heat flow (R-value) is around 7 for every 3 cm thickness of material. PUR boxes are extremely durable, very rigid and reusable. However, PUR is difficult to recycle.



PUR insulated boxes (Sofrigam)

Push system: A distribution system in which the personnel who issue the supplies determine the quantities to be issued. In the push systems, distribution decisions are made by higher-level facilities. The quantities distributed are usually based on usage and stock reports without receiving requisitions. It is better to choose a push system, if programme operations are centralized, data processing and analysis are conducted at the upper levels, the staff at lower levels do not have the management skills to direct a distribution system and the stocks are limited. Also called as “allocation” system. (WHO)

Once the system has been chosen as “push” or “pull”, then the responsibility for providing transport has to be decided. If responsibility is on supplying facility then it is called a distribution system. If receiving facility provides transportation then this is

called a collection or pickup system. Therefore, combination of these systems can be designed depending on the needs of the country.

Possible system designs by decision making and transport responsibilities (WHO)			
		Transportation responsibility	
Decision making responsibility	Requesting facility	Requesting facility	Issuing facility
	Issuing facility	Pull-collection	Pull-distribution
		Push-collection	Push distribution

This management structure may differ at various levels of the system; higher levels may pull and then push to lower levels. Even at a single level, the system may be mixed: a regional warehouse might allocate stock to a health centre quarterly, but the health centre may be able to request additional supplies if needed.



Qualification: Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification. (WHO)

Qualification protocol: A written and approved plan detailing how a qualification will be conducted including test parameters, product characteristics, equipment and acceptance criteria. (WHO)

Qualified person (QP): The regulations specify that no batch of medicinal product can be released for sale or supply prior to certification by a QP that the batch is in accordance with the relevant requirements. The QP is typically a licensed pharmacist, biologist or chemist (or a person with another permitted academic qualification) who has several years of experience working in pharmaceutical manufacturing operations, and has passed examinations attesting to his or her knowledge. The requirement for QP oversight has been extended to material for use in clinical trials since the introduction of EU Directive 2001/20/EC. In countries that are part of PIC/S, “responsible person” and/or “authorized person” terms are used interchangeably.

Qualified third party: An entity independent from the company that is mandated and involved in the preparation, execution or analysis of a quality assurance (QA) activity for the company. This third party should present the adequate professional qualification to perform QA activities. (WHO)

Quality: The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength, and purity (ICH Q6A).

Quality agreement: See *service level agreement*.

Quality assurance: A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development. (WHO)

The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that (WHO):

- Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) and good clinical practice (GCP);
- Production and control operations are clearly specified in a written form and GMP requirements are adopted;
- Managerial responsibilities are clearly specified in job descriptions;
- Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;
- The finished product is correctly processed and checked, according to the defined procedures;
- Pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products;
- Satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;
- There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;
- Deviations are reported, investigated and recorded;
- There is a system for approving changes that may have an impact on product quality;
- Regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

Quality audit: An audit that consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors. (WHO)

Quality by design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. (ICH Q8/R2)

Quality control (QC): The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the product have been fulfilled.

Quality management system (QMS): A set of policies, processes and procedures required for planning and execution in the core business area of organization that can impact organization's ability to meet customer requirements. QMS is not a group of documents, it is an entire system which documents are used to describe the system. ISO 9001:2015 is an example of QMS. The eight QMS principles on which the quality management standards of the ISO 9000 series are based can be used by senior management as a framework to guide their organizations towards improved performance. (ISO)

Quality management principles (ISO 9000:2005 and ISO 9004:2009)

Contents	Principle	Key benefits
1. Customer focus	Organizations depend on their customers and therefore should understand current and future customer needs, should meet customer requirements and strive to exceed customer expectations.	<ul style="list-style-type: none"> Increased revenue and market share obtained through flexible and fast responses to market opportunities Increased effectiveness in the use of the organization's resources to enhance customer satisfaction Improved customer loyalty leading to repeat business.
2. Leadership	Leaders establish unity of purpose and direction of the organization. They should create and maintain the internal environment in which people can become fully involved in achieving the organization's objectives.	<ul style="list-style-type: none"> People will understand and be motivated towards the organization's goals and objectives Activities are evaluated, aligned and implemented in a unified way Miscommunication between levels of an organization will be minimized.

Contents	Principle	Key benefits
3. Process approach	A desired result is achieved more efficiently when activities and related resources are managed as a process.	<ul style="list-style-type: none"> ■ Lower costs and shorter cycle times through effective use of resources ■ Improved, consistent and predictable results ■ Focused and prioritized improvement opportunities.
4. System approach to management	Identifying, understanding and managing interrelated processes as a system contributes to the organization's effectiveness and efficiency in achieving its objectives	<ul style="list-style-type: none"> ■ Integration and alignment of the processes that will best achieve the desired results ■ Ability to focus effort on the key processes ■ Providing confidence to interested parties as to the consistency, effectiveness and efficiency of the organization.
5. Continual improvement	Continual improvement of the organization's overall performance should be a permanent objective of the organization.	<ul style="list-style-type: none"> ■ Performance advantage through improved organizational capabilities ■ Alignment of improvement activities at all levels to an organization's strategic intent ■ Flexibility to react quickly to opportunities.
6. Factual approach to decision making	Effective decisions are based on the analysis of data and information	<ul style="list-style-type: none"> ■ Informed decisions ■ An increased ability to demonstrate the effectiveness of past decisions through reference to factual records ■ Increased ability to review, challenge and change opinions and decisions.
7. Mutually beneficial supplier relationships	An organization and its suppliers are interdependent and a mutually beneficial relationship enhances the ability of both to create value	<ul style="list-style-type: none"> ■ Increased ability to create value for both parties ■ Flexibility and speed of joint responses to changing market or customer needs and expectations ■ Optimization of costs and resources.

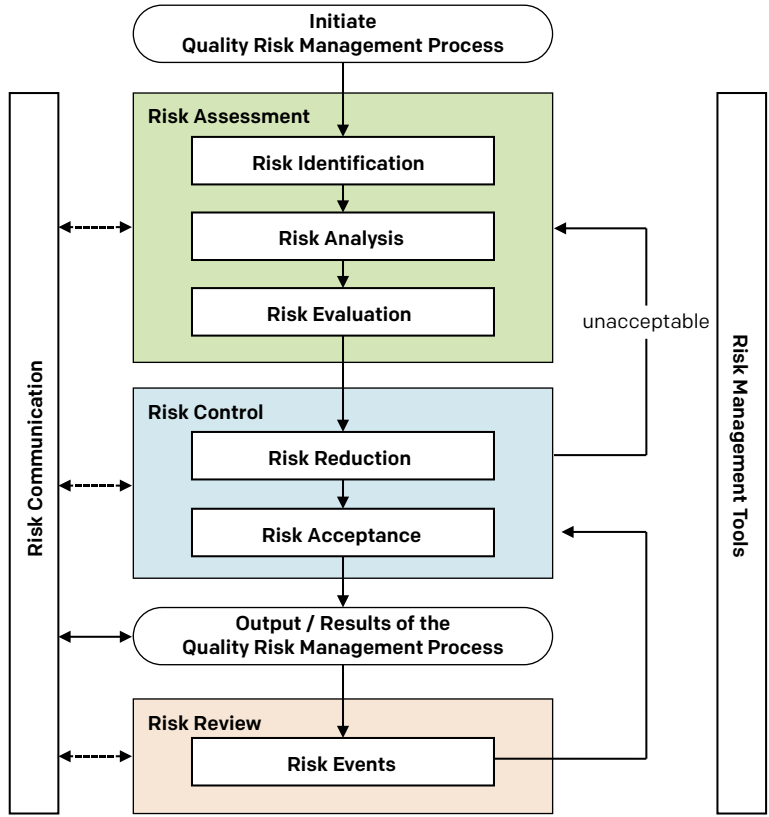
Quality manual: Document specifying the quality management system of an organization. As defined by ICH Q10, quality manual should include the following:

1. The quality policy
2. The scope of the pharmaceutical quality system;

3. Identification of the pharmaceutical quality system processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner;
4. Management responsibilities within the pharmaceutical quality system

Quality risk management: A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle (*ICH Q9*). Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality.

Overview of a typical quality risk management process (ICH Q9)



Quality system: The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met. (*ICH Q9*)

Quality target product profile (QTPP): A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (*WHO*)

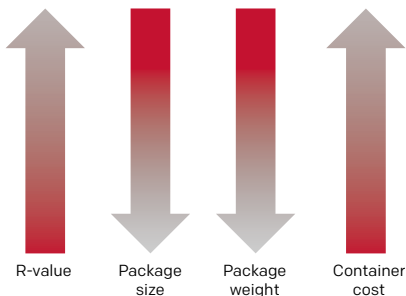
Quantity in hand: The quantity of usable stock in inventory at a given point/period in time.

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection. (*WHO*)

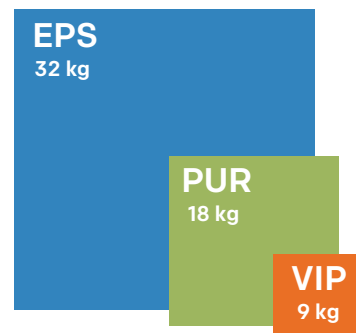
R

R-value (insulation): A measure of thermal resistance, expressed as the ratio of the temperature difference across an insulator and the heat flux (heat transfer per unit area per unit time, Q_A) through it or $R = \Delta T / Q_A$. Although thermal resistance varies with temperature, it is usually treated as a constant value. The higher the value of R, the better is the insulation material's theoretical effectiveness.

The relationship between R-value, package size, package weight and container cost (Kartoglu)



The impact of R-value on the packaging size for 1 litre of payload (Illustrated based on data from Thermosafe)



Radiation: Flow of atomic and subatomic particles and of waves, such as those that characterize heat rays, light rays, and X rays. Radiant energy from the sun warms the Earth.

RAG status: The red, amber or green color designation against pre-determined value range to break the risks into groups requiring different response strategies. Mostly used in two-axis risk score illustration like in PRA/PHA. See *risk scales*.

Random number: A number randomly selected.

Random sampling: A method in which chance alone determines who will be included in the sample, removing any possibility of selection bias.

Randomization: In its simplest form, randomization is a process by which n individuals are assigned to a test (n_T) or control (n_C) treatment so that all possible groups of size $n = n_T + n_C$ have equal probability of occurring. Thus randomization avoids systematic bias in the assignment of treatment. It also promotes balance with respect to known and unknown prognostic factors that could affect the outcome of interest. While it does not guarantee that treatment groups will be exactly equal with respect to these factors, it does guarantee that any imbalance that occurs arose purely by chance. The process of randomization guarantees the validity of statistical analyses of treatment effect and (with adequate sample size) allows the detection, or ruling out, of small or moderate treatment differences. (WHO)

Rate: A ratio that expresses the frequency of a characteristic per 100 (or per 1000, per million, etc.) persons in the population at a given time.

Rate of consumption: The average quantity of stock dispensed to users during a particular time period.

Rational use of medicines: Rational use of medicines requires that “patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community”. Irrational use of medicines is a major problem worldwide. WHO estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them correctly. The overuse, underuse or misuse of medicines results in wastage of scarce resources and widespread health hazards. Examples of irrational use of medicines include: use of too many medicines per patient (“poly-pharmacy”); inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections; over-use of injections when oral formulations would be more appropriate; failure to prescribe in accordance with clinical guidelines; inappropriate self-medication, often of prescription-only medicines;

non-adherence to dosing regimes. (WHO)

WHO advocates 12 key interventions to promote more rational use:

1. Establishment of a multidisciplinary national body to coordinate policies on medicine use
2. Use of clinical guidelines
3. Development and use of national essential medicines list
4. Establishment of drug and therapeutics committees in districts and hospitals
5. Inclusion of problem-based pharmacotherapy training in undergraduate curricula
6. Continuing in-service medical education as a licensure requirement
7. Supervision, audit and feedback
8. Use of independent information on medicines
9. Public education about medicines
10. Avoidance of perverse financial incentives
11. Use of appropriate and enforced regulation
12. Sufficient government expenditure to ensure availability of medicines and staff.

Raw data: All records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, as well as all records of data from automated instruments or exact, verified copies, e.g., in the form of photocopies or microfiches. Raw data can also include photographic negatives, microfilm, magnetic media (e.g., computer diskettes), optical media (CD-ROMs) and computer records. (WHO)

Reactogenicity: Reactions, either local or systemic, that are considered to have a causal relationship to the vaccination. (WHO)

Reagent: A substance other than a starting material, intermediate, or solvent that is used in the manufacture of a new drug substance. (ICH Q3A/R2)

Real-time, real-condition stability studies: Studies on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a vaccine, during and up to the expected shelf-life and storage periods of samples under the expected handling and storage conditions. The results are used to recommend storage conditions, and to establish the shelf-life and/or the release specifications. (WHO)

Recall: A process for withdrawing or removing a pharmaceutical material from the distribution chain because of defects in the materials or complaints of a serious nature. The recall might be initiated by the manufacturer/importer/distributor or a responsible agency. (WHO)

Receiving record: Transaction record that lists the names and quantities of items received. Usually paired with a packing slip.

Records: Records provide evidence that an event took place, an action was performed, or that a decision was made. Often, records are examined when something goes wrong, during an audit, or by a national authority during an inspection. It is essential that records are available and considered by the reader to be reliable and trustworthy. Records can be paper based, like logs or temperature charts, or electronic, like online graphs of temperature conditions.

Refrigerant: A substance or mixture used in a heat pump and refrigeration cycle. In most cycles the refrigerant undergoes phase transitions from liquid to gas or solid and back again.

Refrigerated container or reefer: A thermally insulated shipping container or inter-modal freight container, equipped with an integrated refrigeration unit, used for the transport of TTSPPs, by road, rail or ocean freight. The refrigeration unit requires an external electrical power supply when located at a land based site, on a container ship or on a quay. During road transport electrical power is typically supplied by a diesel generator. (WHO)



A refrigerated container with front and back views (topae, Shutterstock)

Refrigerated vehicle: Road transport vehicle such as a van, truck or semi-trailer whose isolated thermostatically controlled cargo compartment is maintained at a temperature different (lower or higher) than the external ambient conditions. The environment inside the cargo compartment may be *temperature-controlled* or *temperature-modified*. (WHO)



A refrigerated van used for distribution of vaccines in Bursa province, Turkey (Kartoglu)

Refrigeration equipment: The term “refrigeration” or “refrigeration equipment” means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity. (WHO)

Regulation: Written rules adopted by administrative agencies pursuant to authority granted to those agencies under applicable statutes. For example, many countries have statutes that give administrative agencies the authority to establish rules governing the approval of new medications. Pursuant to these statutes, agencies establish rules specifying the standards and procedures under which approval decisions will be made. In some countries, regulatory entities’ authority to inspect clinical trials derives from provisions of administrative regulations (WHO). For example, in 1987, the U.S. Food and Drug Administration, pursuant to authority granted to it by the U.S. Congress, adopted the following regulatory provision:

21 C.F.R. § 312.68 Inspection of investigator’s records and reports.

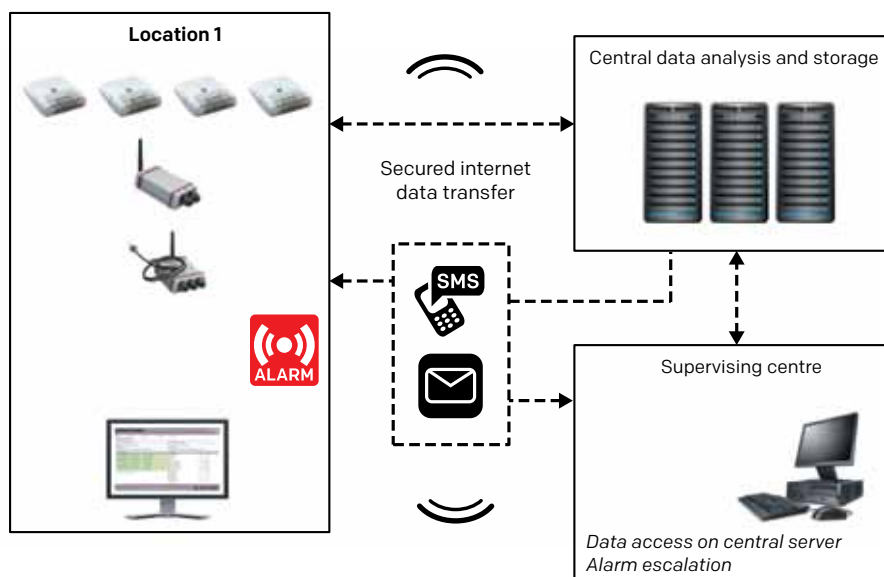
An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to § 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

Relabelling: The process of putting a new label on the material (see also *labelling*). (WHO)

Release specification: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an API or FPP at the time of its release. (WHO)

Remote temperature monitoring: Monitoring temperatures over an IP network.

A typical remote temperature monitoring system (Smartview/Berlinger & Co.)



Reorder level: See *minimum stock level*.

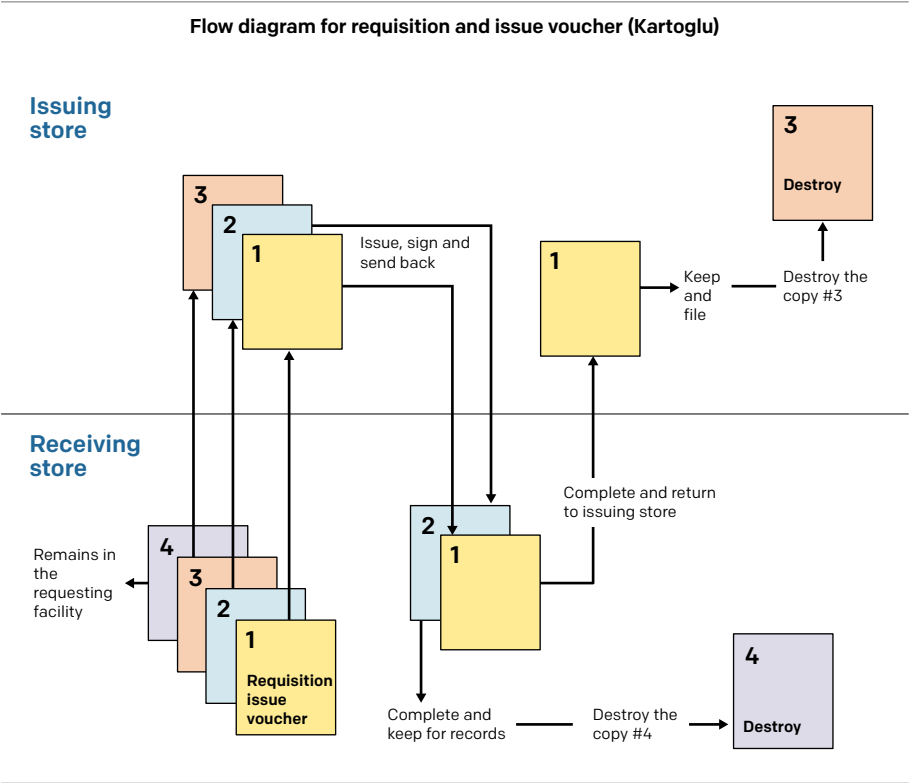
Repackaging: The action of changing the packaging of the material. (WHO)

Reproductive rate: The average number of secondary cases of an infection arising from a single primary case. The measure is inherent to the potential (infectiousness, susceptibility, measures of protection) of a microorganism to spread from person to person in a population. (WHO)

Request indicator: See *minimum stock level*.

Requisition and issue voucher: Transaction record used in a pull distribution system that lists the items and quantities requested by a facility, the quantity actually issued and received. A requisition/issue voucher is similar to an issue voucher; however it is used in requisition/pull systems. Requisition/issue voucher lists the items and quantities requested by a facility. It also includes a column for the quantity actually issued. When issuing store supplies lesser quantity than requested, explanations should be given in remarks column. (WHO)

Requisition/issue voucher should be completed in four copies. The requesting facility completes the form, signs the record and sends the top three copies (1, 2, and 3) to the issuing facility, keeping the bottom copy (4). The issuing facility fills in the order, signs the form, and sends the top two copies (1 and 2) to the receiving facility, along with the supplies, keeping the bottom copy (3) as a reminder. Upon arrival of goods, the receiving facility verifies the quantity received, signs the form and sends back the top copy (1). The receiving facility keeps the second copy (2) for its files and destroys the copy (4) that was kept before. The top copy (1) arrives at the issuing facility, which then issuing facility destroys the reminder (3) and keeps the top copy (1) for its files. At the end, each of the facilities ends up with a completed copy of requisition/issue voucher for filing. Below Figure illustrates the flow of a requisition/ issue voucher.



Sample requisition and issue voucher (WHO)

Voucher no:

Article no	REQUEST				ISSUE					RECEIVE			Remarks
	Com-modity name	Previous month's consumption (doses)	Quantity in hand (doses)	Quantity requested (doses)	Batch number	Expiry date	Freeze indicator	VVM status	Amount (doses)	Freeze indicator	VVM status	Amount (doses)	
A	B	C	D	E	F	G	H	I	J	K	L	M	N
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													

Requesting facility:	<input type="text"/>	Issuing facility:	<input type="text"/>	Receiving facility:	<input type="text"/>
Requested by Name:	<input type="text"/>	Approved by Name:	<input type="text"/>	Received by Name:	<input type="text"/>
Title:	<input type="text"/>	Title:	<input type="text"/>	Title:	<input type="text"/>
Requisition date:	<input type="text"/>	Requisition date:	<input type="text"/>	Requisition date:	<input type="text"/>
Signature:	<input type="text"/>	Signature:	<input type="text"/>	Signature:	<input type="text"/>

Requisition system: See *pull system*.

Research participant: An individual who participates in a biomedical research project, either as the direct recipient of an intervention (e.g., study product or invasive procedure), as a control, or through observation. The individual may be a healthy person who volunteers to participate in the research, or a person with a condition unrelated to the research carried out who volunteers to participate, or a person (usually a patient) whose condition is relevant to the use of the study product or questions being investigated. (WHO)

Reseller: A reseller is a commercial entity, licensed to act on behalf of a Legal Manufacturer, and which carries product liability and warranty responsibilities no less onerous than those carried by the Legal Manufacturer. (WHO)

Residual risk: Risk remaining after all control measures have been taken. It's the risk remaining after you've reduced the risk, removed the source of the risk, modified the consequences, changed the probabilities, transferred the risk, or retained the risk.

Re-test date: The date after which an active API should be re-examined to ensure that the material is still in compliance with the specification and thus is still suitable for use in the manufacture of an FPP. (*WHO*)

Re-test period: The period of time during which the API is expected to remain within its specification and, therefore, can be used in the manufacture of a given FPP, provided that the API has been stored under the defined conditions. After this period a batch of API destined for use in the manufacture of an FPP should be re-tested for compliance with the specification and then used immediately. A batch of API can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most substances known to be labile, it is more appropriate to establish a shelf-life than a re-test period. The same may be true for certain antibiotics. (*WHO*)

Risk: The combination of the probability of occurrence of harm and the severity of that harm (*ISO 14971:2000*).

Risk analysis: The estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk. (*ICH Q9*)

Risk assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and the types of information needed to address the risk question will be more readily identifiable. (*ICH Q9*)

As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk communication: The sharing of information about risk and risk management between the decision maker and other stakeholders. (*ICH Q9*)

Risk control: Actions implementing risk management decisions. (*ISO Guide 73*)

Risk evaluation: The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk. (*ICH Q9*)

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

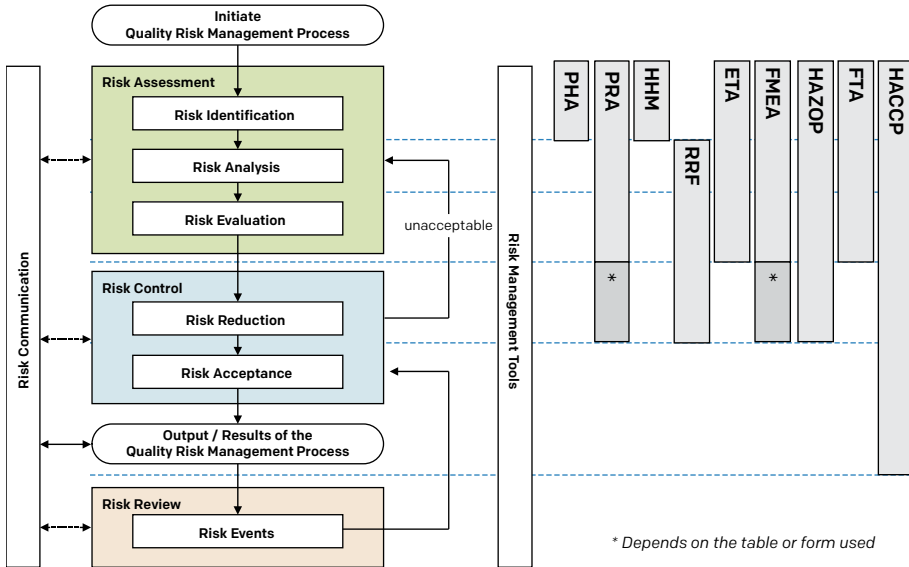
Risk identification: The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description. Risk identification addresses the “What might go wrong?” question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process. (*ICH Q9*)

Risk management: The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk. (*ICH Q9*)

Risk management framework: A set of components that support and sustain risk management throughout an organization (*ISO 31000*). In risk management framework there are two types of components: foundations and organizational arrangements. Foundations include risk management policy, objectives, mandate, and commitment. And organizational arrangements include the plans, relationships, accountabilities, resources, processes, and activities used to manage organization’s risk.

Risk management process: One that systematically applies management policies, procedures, and practices to a set of activities intended to establish the context, communicate and consult with stakeholders, and identify, analyze, evaluate, treat, monitor, and review risk. (*ISO 31000*)

Risk management process and tools to use (J Vesper)



Risk matrix: A matrix that is used during risk assessment to define the various levels of risk as the product of the harm probability categories and harm severity categories. The two-criterion model of severity and probability based matrix is a typical risk matrix. See *risk scales*.

Example of two-factor risk matrix

		PROBABILITY		
		Low	Medium	High
SEVERITY	High potential impact	Medium risk	High risk	High risk
	Medium potential impact	Medium risk	Medium risk	High risk
	Low potential impact	Low risk	Low risk	Medium risk

Tabular representation of risk levels (J Vesper)

		SEVERITY			
		I Catastrophic	II Critical	III Marginal	IV Negligible
PROBABILITY	A) Frequent	Design action is required to eliminate or control hazard	Design action is required to eliminate or control hazard	Design action is required to eliminate or control hazard	Negligible hazard
	B) Probable	Design action is required to eliminate or control hazard	Design action is required to eliminate or control hazard	Hazard must be controlled or hazard probability reduced	
	C) Occasional	Design action is required to eliminate or control hazard	Hazard must be controlled or hazard probability reduced	Hazard control desirable if cost effective	
	D) Remote	Hazard must be controlled or hazard probability reduced	Hazard control desirable if cost effective	Hazard control desirable if cost effective	
	E) Improbable	Assume will not occur			
	F) Impossible	Impossible occurrence			

For likelihood (probability), the move has been to have terms that are more “observable” or “countable”.

An example of occurrence scale (adapted by J Vesper)

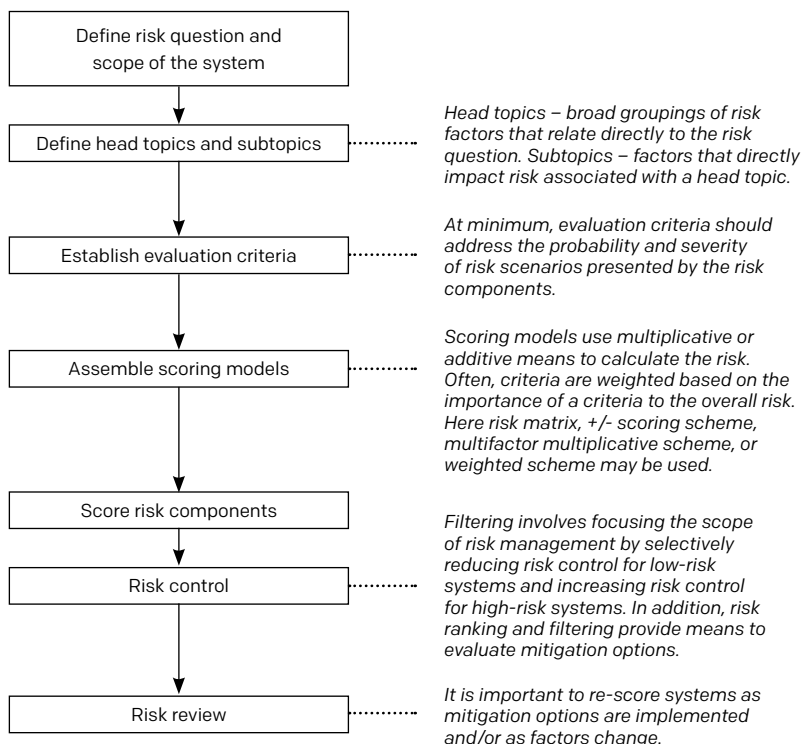
No.	Term	Short definition	Long definition	Probability (six sigma)
1	Remote	Failure is unlikely if not impossible	1 occurrence in more than 5 years or fewer than 2 occurrences in 1 billion events	<2 per 1 billion
2	Low	Failures few and far between	1 occurrence every 3 to 5 years or fewer than 3 occurrences in 10 million events	<3 per 10 million
3	Low	Relatively few failures	1 occurrence every 1 to 3 years or 6 occurrences in 1 million events	<6 per million
4	Low	Infrequent failures	1 occurrence per year or 6 occurrences in 100,000 events	<6 per 100,000
5	Moderate	Occasional failures	1 occurrence every 6 to 12 months or 1 occurrence in 10,000 events	<1 per 10,000
6	Moderate	Frequent failures	1 occurrence every 3 to 6 months or 3 occurrences in 1,000 events	<0.03%
7	Moderate	Failures occur often	1 occurrence every month or 1 occurrence in 100 events	<1%
8	High	Repeated failures	1 occurrence per week or 5 occurrences in 100 events	<5%
9	High	Failures occur more often than not	1 occurrence 3-6 days or 3 occurrences in 10 events	≤30%
10	High	Failures is almost inevitable	1 or more occurrences every 1 or 2 days or more than 3 occurrences every 10 events	>30%

Risk ranking and filtering (RRF): Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives. (*ICH Q9*)

Risk ranking and filtering can be used to develop standardized risk rating forms prioritize vendor or contractor sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework. Limitations of RRF include that only risks included in the

filtering get examined and that creating risk rating forms takes significant time of subject matter experts.

Risk ranking and filtering process (Kartoglu)



Risk reduction: Actions taken to lessen the probability of occurrence of harm and the severity of that harm. (ICH Q9). See also *risk treatment*.

Risk review: Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk. (ICH Q9)

Risk scales (used in risk assessment): As for quantitative risk assessment tools, risk scales used for rating the severity of consequence, likelihood of occurrence and detectability should be clearly articulated. This is important to appropriate levels of differentiation in order to support meaningful risk prioritization. It also helps for consistency across the risk profile attributes to ensure that all attributes proportionally contribute to the overall prioritization of the risk. Risk scales (definitions, levels and numbers) may vary depending on the system under evaluation.

In order to appropriate levels of differentiation, five-point rating scales are widely used. Use of non-consecutive numbers (e.g., 1, 3, 5, 7, 10) are more useful compared to use of consecutive numbers (e.g., 1, 2, 3, 4, 5) in scales since non-consecutive numbers are proven to be less useful in differentiation. In the case of the desire to put more emphasis on the severity criteria, alternative a non-linear scoring scale can be utilized (e.g., 1, 4, 9, 16, 25).

Examples of risk scales for FMEA* (modified from PQRI)

SEVERITY OF CONSEQUENCE		
Value	Description	Criteria
1	Irrelevant	No impact to product quality and process robustness
4	Slight	No impact on product quality
9	Important	Noticeable impact on product quality, but can be recovered by reprocessing
16	Critical	Definite impact to product quality that may require rework
25	Disastrous	Batch failure, not recoverable by rework
LIKELIHOOD OF OCCURRENCE		
Value	Description	Criteria
1	An unlikely probability	Failure has never been seen in any relevant lab experiments, or scale-up batches yet but it is theoretically possible.
3	A remote probability	Failure only seen once or twice in relevant lab experiments, never in scale-up batches.
5	An occasional probability	Failure potential has been noted in several relevant lab experiments, or at scale-up. If procedures are followed the failure potential is minimal.
7	A moderate probability	Failure potential has been noted in several relevant lab experiments, or at scale-up, in-process control maybe required to avoid failure.
9	A high probability	Failure potential has been noted in several relevant lab experiment, or at scale-up, an active non-standard feedback control loop may be required.
DETECTABILITY		
Value	Description	Criteria
1	High degree of detectability	A: Validated automatic detection system that is a direct measure of failure. B: Two or more manual operated validated detection systems, direct or indirect. (e.g., Control range and IPC)
3	Good detectability	A: Single manually operated validated detection system that is a direct measure of failure. (e.g., IPC of failure, validated PAT)
5	Likely to detect	A: Single manually operated validated detection system that is not a direct measure of failure. (e.g., PAT measurements or IPC's not directly linked to failure)
7	Fair detectability	A: Non validated (manual or automated) detection. (e.g., visual level check, visual inspection of vessels).
9	Low or no detectability	No ability to detect the failure

*The above definitions for Severity of consequence, Likelihood of occurrence and Detectability were developed for a FMEA involving a new process development; these will change based on the subject under assessment.

As for PRA/PHA where in general likelihood of occurrence and severity of consequence are rated and risk score is calculated based on these two criteria, response strategies can be illustrated using a matrix and traffic light system by assigning red, amber or green against pre-determined value range. This breaks the risks into groups requiring different response strategies. This color designation is also known as “RAG status”.

As same linear scales can be used for both likelihood of occurrence and severity of consequence, a doubled risk scale may be used especially for severity element as it gives more weight to risks with a high impact. A risk with a low probability but a high impact is thus viewed as much more severe than a risk with a high probability and a low impact. This avoids any averaging out of serious risks.

Linear and doubled risk scales used in PRA/PHA

		SEVERITY				
		1	2	3	4	5
PROBABILITY	5	5	10	15	20	25
	4	4	8	12	16	20
	3	3	6	9	12	15
	2	2	4	6	8	10
	1	1	2	3	4	5

Linear risk scale

		SEVERITY				
		1	2	4	8	16
PROBABILITY	5	5	10	20	40	80
	4	4	8	16	32	64
	3	3	6	12	24	48
	2	2	4	8	16	32
	1	1	2	4	8	16

Doubled risk scale

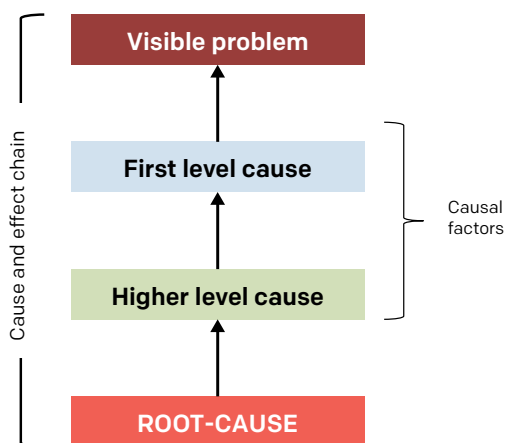
In this regard, red risks are unacceptable and have the priority in response strategy. Amber risks are moderate risks having secondary priority while green risks are acceptable (but this does not mean they can be ignored - they should be addressed at least through means of contingency). See also *risk matrix*.

Risk treatment: The process of selecting and implementing of measures to modify risk. Risk treatment measures can include avoiding, reducing, optimizing, transferring or retaining risk. Once the treatment is being implemented, it becomes a control and/or it modifies existing controls. ISO 31000:2009 gives a list on how to deal with risk:

- Avoiding the risk by deciding not to start or continue with the activity that gives rise to the risk
- Accepting or increasing the risk in order to pursue an opportunity
- Removing the risk source
- Changing the likelihood
- Changing the consequences
- Sharing the risk with another party or parties (including contracts and risk financing)
- Retaining the risk by informed decision

Root-cause: A factor considered if removal thereof from the problem-fault-sequence prevents the final unwanted event from recurring. Root-cause is the “evil at the bottom” setting in motion the whole cause and effect chain.

Root-cause within the cause and effect chain (Kartoglu)



Root-cause analysis: A collective term that describes a wide range of approaches, tools, and techniques used to uncover the root causes or faults or problems. Root cause analysis must be performed systematically, usually as part of an investigation, with conclusions and root causes that are identified with documented evidence, which requires typically a team effort. There might be more than one root-cause for an unwanted event. The root cause(s) identified depends on the way in which the visible problem is defined. Effective problem statements and descriptions are important to ensure the execution of appropriate analyzes. There are various approaches that can be used in root-cause analysis: such as 5 whys, appreciation (so what tech-

nique), drill-down, cause and effect diagrams (fish-bone diagram, fault tree analysis), and failure mode effects analysis.

Route of administration: The means by which the candidate [vaccine] product is introduced to the host. Possible routes of administration include the intravenous, intramuscular, subcutaneous, transcutaneous, intradermal, transdermal, oral, intranasal, intranodal, intravaginal and intrarectal routes. (*WHO*)

S

Safety and tolerability: The safety of a medical product concerns the medical risk to the subject, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and hematology), vital signs, clinical adverse events (diseases, signs and symptoms), and other special safety tests (e.g., electrocardiograms, ophthalmology). The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject. (*ICH Q9*)

Safety stock: The amount of stock (number of months' supply) below the minimum level which serves as a cushion or buffer against major fluctuations in product demands or unexpected shipment delays. The safety stock is the reserve stock used to protect against stock outs due to delivery delays, product shortages at the supplier level, or when stock is dispensed at an unexpectedly high rate. The level of safety stock required is usually different for each programme and should be based on past consumption data. (*WHO*)

Sample size: The optimum number of subjects to be recruited to answer the main objective(s) of the study.

Seasonal packaging solution: (Also called a dedicated packaging solution). A packed shipping container system, whose effective performance in different seasons requires more than one packing configuration. These configurations depend on seasonal variants such as summer and winter or hot and cold season exposure. (*WHO*)

Secondary attack-rate study: An outbreak investigation in a defined susceptible population. The population to be studied is either a cluster (in an urban or semi-urban

setting) or a household (or family). Outbreak investigations may be either observational or experimental. The unit of randomization may be the individual, a household or a cluster. (*WHO*)

Secondary pack or carton or market package: The package presentation intended for the end-user (e.g., bottle + cap liner + dose cap + leaflets + carton) but not including packaging used solely for transport purposes (e.g., *Tertiary carton* or *Insulated shipper*). The secondary pack may contain multiple units of product. (*WHO*)

Sedimentation rate: A measure of the particles in freeze sensitive aluminium adjuvanted vaccines sedimenting in a tube over a given period of time, expressed in percentage. The shake test is based on the difference or similarity of sedimentation rates of purposely frozen a control vial and a test vial. Frozen samples of same vaccines precipitated minimum of 2 times faster than their non-frozen equivalents. The highest precipitation coefficient was found in one of the WHO prequalified DT vaccines (15 times faster). See also *precipitation coefficient* and *shake test*.

Semi-permeable containers: Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by adsorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles and vials.

Sensitivity: Test's ability to correctly detect patients without a condition. Also called "true negative rate". Also see *validity*.

Sensor: A mechanical device (pressure switch, or bimetal temperature switch, a digital or analogue transducer (limit switch, pressure sensor, temperature sensor, etc.) that generates an electrical or mechanical signal to an instrument or a controller in order to be interpreted. (*WHO*)

Serious adverse event or adverse drug reaction: During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions which, in their most se-



**Round LDPE
bottle droppers**

vere forms, threaten life or function. Such reactions should be reported promptly to regulators. (*WHO*)

Therefore, special medical or administrative criteria are needed to define reactions that, either due to their nature ("serious") or due to the significant, unexpected information they provide, justify expedited reporting. To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

After reviewing the various regulatory and other definitions in use or under discussion elsewhere, the following definition is believed to encompass the spirit and meaning of them all:

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- *results in death,*
- *is life-threatening,*

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- *requires inpatient hospitalisation or prolongation of existing hospitalisation,*
- *results in persistent or significant disability/incapacity, or*
- *is a congenital anomaly/birth defect.*

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Serious AEFI: AEFI cases that include death, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect or are life-threatening. (*WHO*)

Seroconversion: Predefined increase in antibody concentration, considered to correlate with the transition from seronegative to seropositive, providing information on the immunogenicity of a vaccine. If there are pre-existing antibodies, seroconversion is defined by a transition from a predefined low level to a significantly higher defined level such as a fourfold increase in geometric mean antibody concentration. (*WHO*)

Service delivery point: Any facility that serves clients directly and where clients (users) receive supplies. Service delivery points are frequently health posts and centres, clinics and hospitals. (*WHO*)

Service delivery problems: Failures identified during the analysis of the patient safety incident, which are associated with the way a service is delivered and the decisions, procedures and systems that are part of the whole process of service delivery. Service delivery problems are usually due to latent failures that arise from well-intentioned but (with hindsight) wrong management decisions that go unrecognized. (*CA Vincent*)

Service level agreement (SLA): A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum-level performance, operation or other service attributes. (*IATA*)
SLA is also known as "quality agreement" and "technical agreement".

Session size: Number of children immunized in a session. Session size is a critical factor influencing the wastage rate in opened vials. Small session size increases wastage if larger dose presentations are used. However, the opening of a new vial, even for one child, in order to avoid a missed opportunity, is always a promoted practice and should not be considered undesirable. (*WHO*)

Severity: A measure of the possible consequences of a hazard. (*ICH Q9*)

Shake test: A test that is designed to determine whether aluminium adsorbed vaccines have been damaged by freezing. Whenever it is suspected that vaccine has been exposed to freezing temperatures, at least one member of the duty personnel in every facility that stores vaccine should know how to perform and interpret the test reliably and correctly. Vaccine which fails the shake test should not be distributed or administered. (WHO)

The shake test currently applies to the following vaccines:

- DT
- DTP
- DTP-HepB
- DTP-HepB+Hib lyophilised
- DTP-HepB-Hib liquid
- DTP-Hib
- Hepatitis B
- Hib liquid
- HPV
- Pneumococcal
- Td
- TT

After freezing, the bonds between the aluminium adsorbent and the antigen in a vaccine are broken. Separated adsorbent tends to form larger, heavier granules that gradually settle at the bottom of the vial when this is shaken. Sedimentation occurs faster in a vaccine vial which has been frozen than in a vaccine vial from the same manufacturer which has never been frozen. When carried out correctly the shake test has been shown to have 100% sensitivity and 100% specificity and 100% positive predictive value.

Under the phase contrast microscope, non-frozen vaccines show uniform fine grain structure while frozen vaccines show large conglomerates of large precipitates with variable structures.

In order the physical structure to be destroyed, solid freezing must take place. When vaccines are slushy frozen, their phase contrast microscopy shows identical images to vaccines that are kept at optimum temperatures. Slushy frozen vials also pass the shake test.

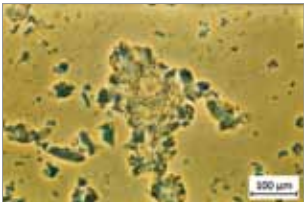


Freeze damaged and non-frozen monodose TT vaccine in shake test (Kartoglu)

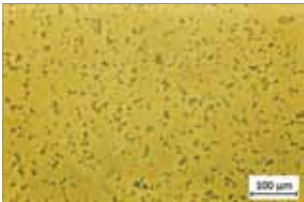
Phase contrast microscopy findings using study vials of various vaccines kept at different temperatures



Fine-grain structure of DTP-HepB vaccine kept between 2°C to 8°C

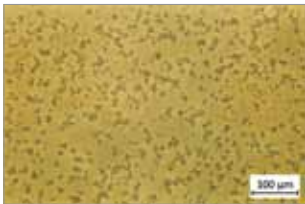


Conglomerates of large precipitates with crystalline structure of dT vaccine affected by freezing -25°C



Fine-grain structure of DTP-HepB vaccine exposed to -2°C for 24 hours

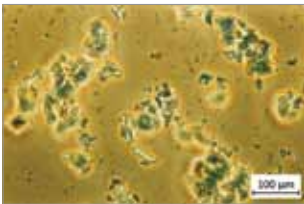
Slushy frozen vials produce identical images with non-frozen samples



Fine-grain structure of HepB vaccine exposed to -10°C until slushy (not fully) frozen

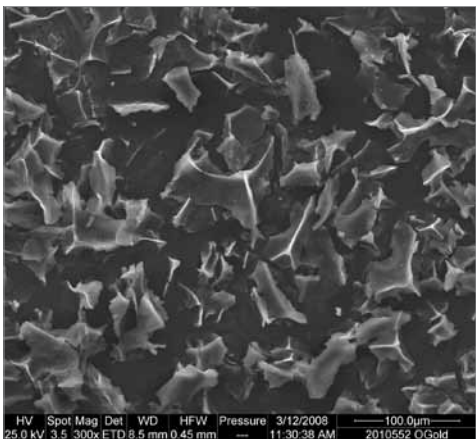


Fine-grain structure of HepB vaccine kept between 2°C to 8°C

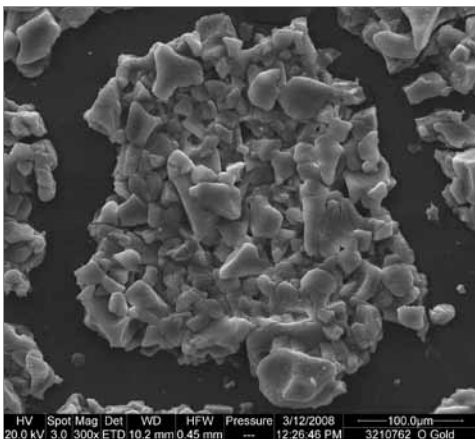


Conglomerates of large precipitates with crystalline and solid structure of HepB vaccine affected by freezing (-10°C, solidly frozen)

Scanning electron micrographs of gold coated conglomerates of frozen HepB, and DTP-HepB vaccines exposed to -25°C for 24 h



HepB vaccine with rough surfaces of precipitate



DTP-HepB vaccine with smooth surfaces of precipitate

If a freeze indicator or other temperature monitoring device shows a freeze alarm, or if you suspect that freezing has occurred, then the shake test must be done to confirm the status of the vaccine. The shake test need not be conducted under the following circumstances; instead the vials must be discarded:

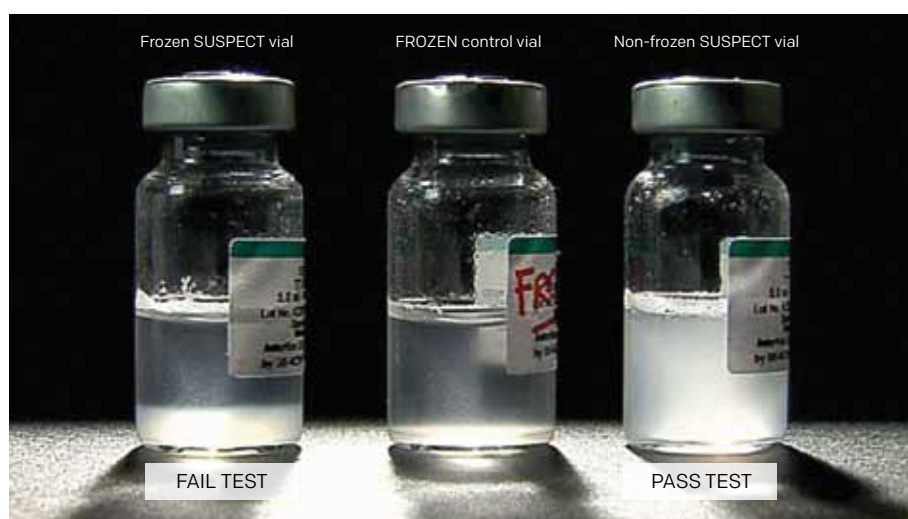
- When solid frozen vaccine vial(s) have been found.
- With a vial for which a homogeneous solution CANNOT be obtained after vigorous shaking. In such cases, the white lumps or sediment cannot be separated from the walls of the glass vial. This happens only with DTP and its combinations vials that are exposed to sub-zero temperatures without freezing (due to P component).



DTP vaccine exposed to sub-zero temperatures without freezing (Kartoglu)

Individual batches of vaccine may behave differently from one another. Therefore the test procedure described below should be repeated with *all* suspect batches.

The method for selecting the *test sample* depends upon the number of vials you suspect have been frozen and whether or not the vaccine has already been accepted from the supplier. If there are a large number of suspect vials, for example, in a cold room or a large refrigerator, you should follow the sampling procedure described



Shake test with a fail and a pass test results (U. Kivanc)

in MIL-STD-105E or, a similar sampling standard, in order to establish the extent of the problem. See *MIL-STD-105E*.

If the test procedure shows that the *test sample* has been damaged by freezing, you must notify your supervisor immediately. You should then follow the procedure set out below to ensure that all of the damaged vaccine is identified and that none of this damaged vaccine is distributed or used.

Shake test protocol

NOTES: <u>This protocol must not be altered.</u> There is only one correct way to conduct a Shake Test. ■ The test procedure described below should be repeated with all suspect batches. In the case of international arrivals, the shake test should be conducted on a random sample of vaccine. However, if there is more than one lot in the shipment, the random sample must include a vial taken from each and every lot.	
1. Take a vial of vaccine of the same type and batch number as the vaccine you want to test, and made by the same manufacturer.	
2. Clearly mark the vial as "FROZEN."	
3. Freeze the vial in a freezer or the freezing compartment of a refrigerator until the contents are completely solid.	
4. Let it thaw. Do NOT heat it!	
5. Take your "TEST" vial from the batch that you suspect has been frozen.	
6. Hold the "FROZEN" vial and the "TEST" vial together in one hand.	
7. Shake both vials vigorously for 10-15 seconds.	
8. Place both vials on a flat surface side-by-side and start continuous observation of the vials until test is finished. (NOTE: If the vials have large labels, which conceal the vial contents, turn both vials upside down and observe sedimentation in the neck of the vial.)	
Use an adequate source of light to compare the sedimentation rates between vials.	
IF,	
9. The TEST vial sediments slower than the FROZEN vial, this is a PASS test. THEN,	10. Sedimentation is similar in both vials OR The TEST vial sediments faster than the FROZEN vial. This is a FAIL test. THEN,
11. Use the vaccine batch.	11. <u>Vaccine damaged:</u> Notify your supervisor. Set aside all affected vaccine in a container marked "DAMAGED VACCINE FOR DISPOSAL – DO NOT USE"
	12. Discard all affected vaccine once you have received permission to do so
	13. Fill in the Loss/Adjustment Form.

Shelf-life: The period of time during which a product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch. Shelf-life is used for the final product; storage period is used for the intermediates. (WHO)

Shelf-life specifications: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that an FPP should meet throughout its shelf life (should not be confused with “release specification”). (WHO)

Shipping indicators: (Electronic) Shipping indicators are single-use devices designed to monitor vaccine temperature during international shipment from the manufacturer to the primary store. Although as a general category, damage indicators including threshold indicators are also considered as shipping indicators, WHO recommends use of 10 or 20 day electronic shipping indicators in each and every shipping carton. These devices serve as a quick reference to help recipient countries determine whether the shipment – or parts of the shipment – have been exposed to temperatures at which vaccines could have been damaged; and help the procurement agency determine when, where, and to what extent temperature limits have been exceeded. (WHO)

They come either with or without USB port (PDF downloadable). All 10 and 20-day electronic shipping indicators have an LCD screen for easy reference.



Various WHO PQS prequalified electronic shipping indicators

In general, shipping indicators are affixed on a waterproof backing card both to include information about the accompanied shipping as well as guidance to the recipient. There are two types of WHO recommended electronic shipping indicators to accommodate different characteristics of vaccines.

Type 1 shipping indicator is configured for freeze-sensitive vaccines and come with three pre-set alarms:

Type 1 shipping indicator alarm settings (WHO)		
Temperature	Alarm type	Period for triggering the alarm
45°C	single event	1 hour
30°C	cumulative	10 hours
-0.5°C	single event	1 hour

Type 2 shipping indicator is configured for lyophilized vaccines and OPV and come with three pre-set alarms:

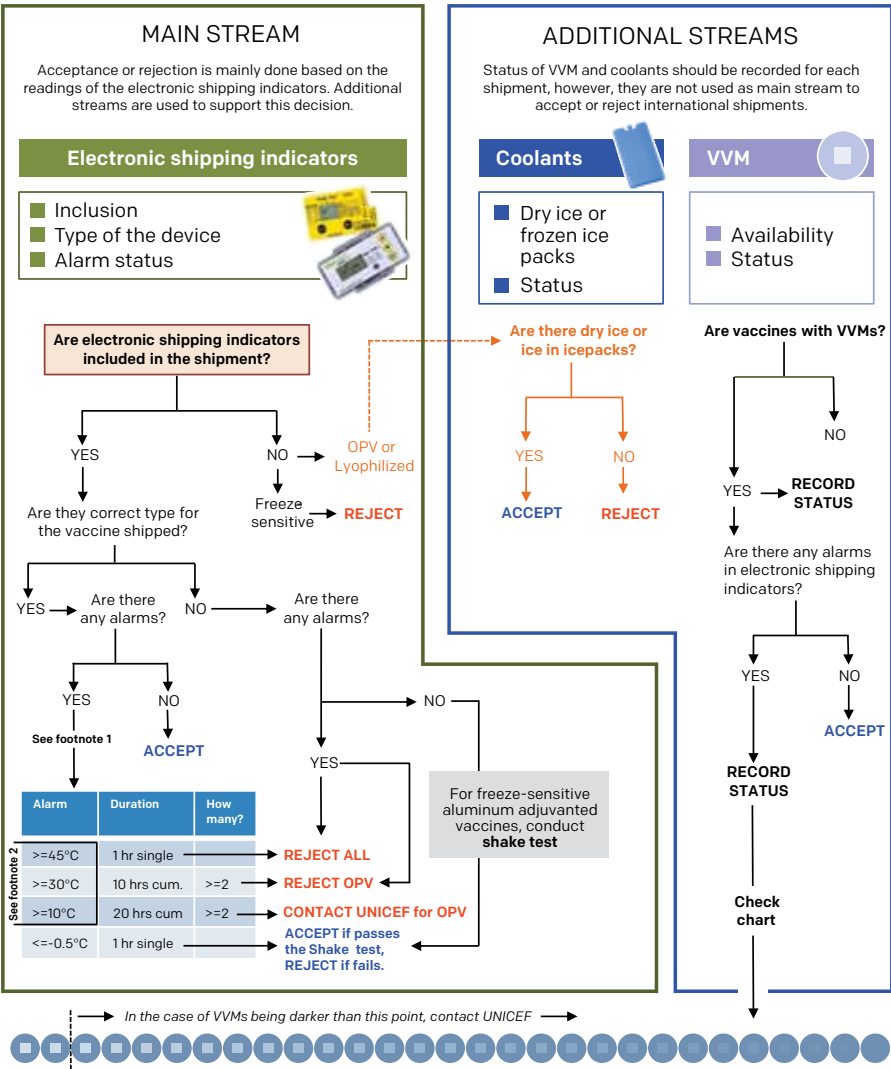
Type 2 shipping indicator alarm settings (WHO)		
Temperature	Alarm type	Period for triggering the alarm
45°C	single event	1 hour
30°C	cumulative	10 hours
10°C	cumulative	20 hours

As for the interpretation of electronic shipping indicators, the following flow must be followed:

Accept or Reject: Interpretation of electronic shipping indicators (Kartoglu/EPELA)

ACCEPT or REJECT

This decision tree assumes that the vaccine type/expiry, quantities received match with what has been ordered and indicated on the shipping documents, as well as all relevant lot release certificates/test protocols from the regulatory authority of the manufacturing country and any other requirements mentioned in the contractual agreement have been met. The decision tree below focuses on the verification of the cold chain conditions maintained throughout the period of transportation.



Shipping lane: The route used for transporting products by different routes of transportation, including air, land, and sea. Shipping lanes originally referred to the path that sailing ships would take aided by prevailing winds and sea currents. More recently, the concept has been expanded to include transportation routes in general. Sometimes the shipping lane from the drug manufacturer to distributor to final user includes a variety of transportation modes: air cargo planes, trucks (or lorries), and even motorcycles. Knowing the shipping lane to be used – and the environmental conditions that might be encountered – helps those designing packaging select the right materials and temperature control methods. (*WHO*)

Shipping system: All components constituting a completed package including: the outer shipping container, all internal ancillary packaging components and temperature-stabilizing medium. (*WHO*)

Signal (safety signal): Information (from one or multiple sources) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. (*CIOIMS*)

Significant change: In general “significant change” for an FPP is defined as the following (*WHO*):

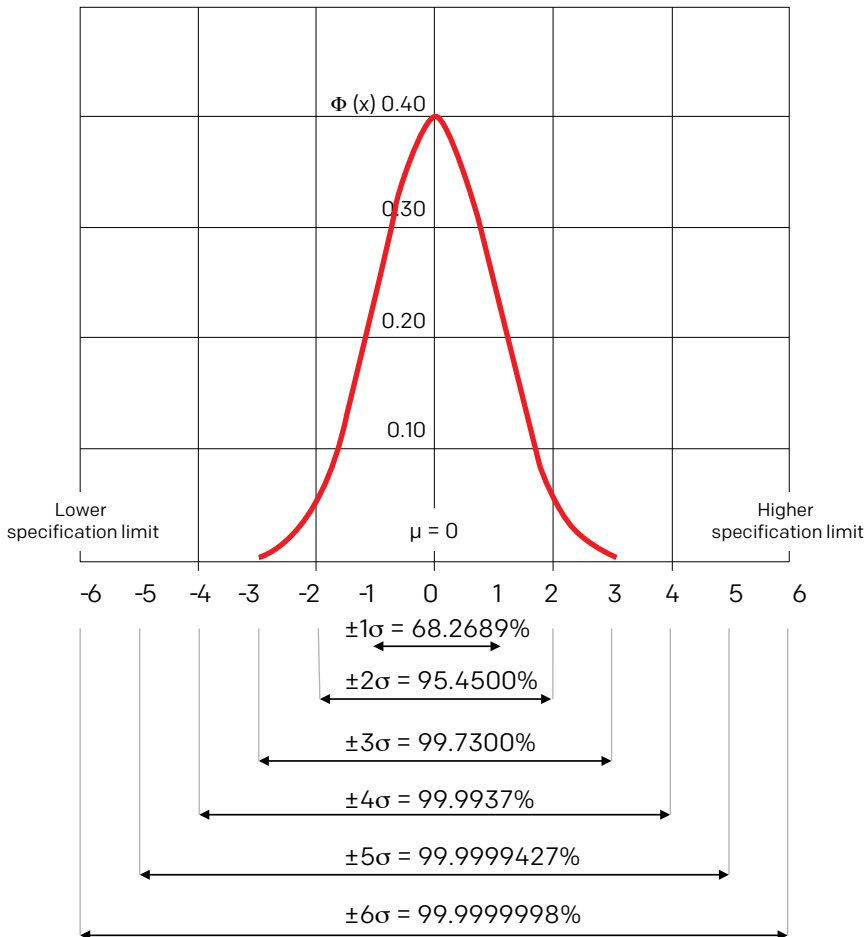
- A 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (*Note:* other values may be applied, if justified, to certain products, such as multivitamins and herbal preparations.)
- Any degradation product exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g., color, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g., softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions. Also, as appropriate for the dosage form:
- Failure to meet the acceptance criterion for pH; or
- Failure to meet the acceptance criteria for dissolution for 12 dosage units.

Six sigma: A well-structured, data-driven methodology for eliminating defects, waste, or quality control problems of all kinds in manufacturing, service delivery, management, and other business activities. Six Sigma methodology and management strategies provide an overall framework for organizing companywide quality control efforts. The term “six sigma process” comes from the notion that when there are six standard deviations between the process mean and the nearest specification limit, practically no items will fail to meet specifications.

Processes that operate with “six sigma quality” over the short term are assumed to produce long-term defect levels below 3.4 defects per million opportunities (DPMO). Six Sigma’s implicit goal is to improve all processes, but not to the 3.4 DPMO level necessarily.

Six sigma projects follow two project methodologies composed of six phases each. DMAIC (define, measure, analyze, improve, and control) is used for projects aiming to improving and existing process, while DMADV (define, measure, analyze, design, and validate) is used for projects aiming to creating new product and/or processes. DMADV methodology is also known as “design for six sigma (DFSS)”.

Normal distribution graph, which underlies the statistical assumptions of the Six Sigma model (Kartoglu)



Six sigma involves absolute professionalizing of quality management functions. Formal programmes adopt a terminology similar to martial arts systems to define a special career path which includes all business functions and levels in the organization: Executive leadership, champions, master black belts, black belts, and green belts.

Solar array: A set of solar photovoltaic modules (panels) electrically connected and mounted on a supporting structure. (WHO)

Solar direct-drive refrigerator: A refrigerator that use solar energy to freeze water or other phase-change material. This stored energy is then used to provide continuous cooling, even when solar irradiance is unavailable or limited (e.g., at night or on cloudy days). (WHO)

Solar irradiance: The amount of solar energy that arrives at a specific area at a specific time. (WHO)

Solar module: A packaged, connected assembly of solar cells. Also known as a solar panel. (WHO)

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance. (ICH Q3A/R2)

Source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (WHO)

Source documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial). (WHO)

Spare parts: Parts that are available and may be used to replace or modify equipment components. (WHO)

Specific and proportional vaccine wastage rates: Specific rates reveal the types behind the overall vaccine wastage, because always unopened vial-specific vaccine wastage rate plus opened vial-specific vaccine wastage rate equals the vaccine wastage rate. (WHO)

However, unopened and opened vial proportional vaccine wastage rates do not equal the vaccine wastage rate. Proportional rates are mistakenly used by many programmes as if they reflect the “service delivery level” vaccine wastage. The denominator in proportional rates includes only the vials you calculate the proportional wastage. For example in proportional vaccine wastage rate in opened vials calculation, the denominator is doses opened for use, whereas the denominator for unopened vials proportional wastage rate is total number of doses unopened doses handled during the period. This is why; these two proportional rates cannot give the overall vaccine wastage rate.

$$\text{Unopened vial specific vaccine wastage rate} = \frac{\text{Doses discarded unopened}}{\text{Start balance} + \text{Doses received} - \text{End balance}} \times 100$$

$$\text{Opened vial specific vaccine wastage rate} = \frac{\text{Doses opened for use} - \text{number of children immunized}}{\text{Start balance} + \text{Doses received} - \text{End balance}} \times 100$$

$$\text{Proportional vaccine wastage rate in unopened vials} = \frac{\text{Doses discarded unopened}}{\text{Start balance} + \text{doses received} - \text{doses opened for use}} \times 100$$

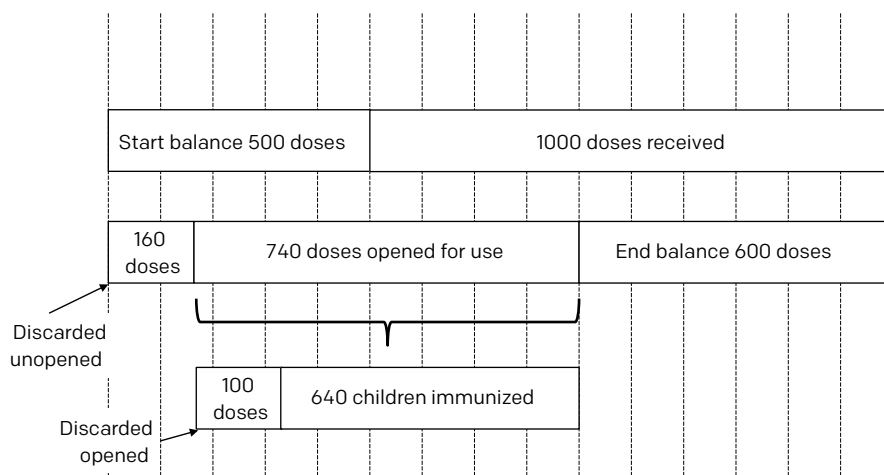
$$\text{Proportional vaccine wastage rate in opened vials} = \frac{\text{Doses opened for use} - \text{number of children immunized}}{\text{Doses opened for use}} \times 100$$

Let's illustrate this by referring to the following example:

Description	Unit
Start balance (1 July)	500 doses
Doses received during July	1000 doses
Doses discarded unopened during July	160 doses
Doses opened for use during July	740 doses
Number of children immunized in July	640 children
End balance (end of July)	600 doses

The below figure gives graphical illustration of these figures:

Calculation of detailed vaccine wastage at the service level



Substituting these figures in the formulas:

$$\text{Vaccine usage rate} = \frac{640}{500 + 1000 - 600} \times 100 = 71\%$$

$$\text{Vaccine wastage rate} = 100 - 71 = 29\%$$

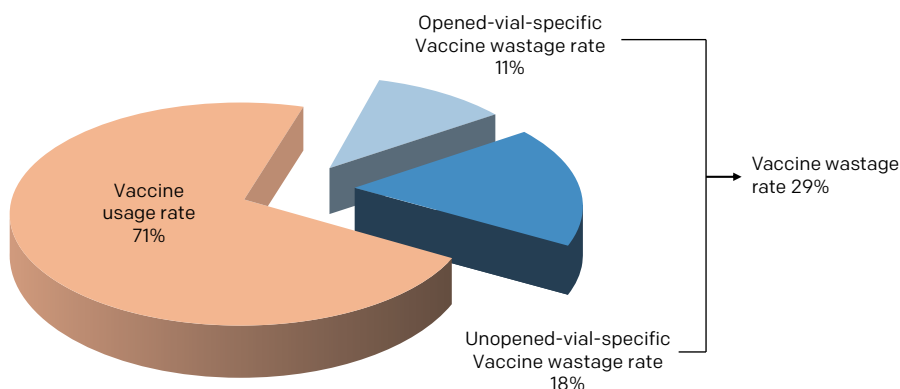
$$\text{Unopened vial specific vaccine wastage rate} = \frac{160}{500 + 1000 - 600} \times 100 = 18\%$$

$$\text{Opened vial specific vaccine wastage rate} = \frac{740 - 640}{500 + 1000 - 600} \times 100 = 11\%$$

$$\text{Proportional vaccine wastage rate in unopened vials} = \frac{160}{500 + 1000 - 740} \times 100 = 21\%$$

$$\text{Proportional vaccine wastage rate in opened vials} = \frac{740 - 640}{740} \times 100 = 14\%$$

The relationship between vial specific wastage rates and overall wastage and vaccine usage (Kartoglu)



Proportional vaccine wastage rates in unopened and opened vials cannot be merged. Proportional vaccine wastage in opened vials (14%) is far below from the real overall vaccine wastage which is 29%, because this rate is proportional and does not include any other wastage occurring in unopened vials. This is why proportional wastage rates cannot and should not be used in routine monitoring of wastage rates. They are useful only in special circumstances especially in understanding the session organization success (opened vials) and stock management (unopened vials).

For further details please refer to “Kartoglu, U. Monitoring vaccine wastage at country level: Guidelines for programme managers. WHO/V&B/03.18” at <http://goo.gl/x2VSdu>

Specific attack rate: A rate that applies to a specific demographic subgroup, e.g., individuals of specific age, sex, or race, giving the total number of events in relation only to that subgroup. Specific attack rates are calculated to identify persons in the population who are at a higher risk of becoming ill than others.

Specific rate: When the numerator and the denominator of a rate are confined to a specific category (e.g., males, children under 5, Asians, etc.) it is referred to as a specific rate; e.g., age-specific death rate, or sex specific morbidity rate.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests

described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities. (*ICH Q6A*)

Specificity: Test's ability to correctly detect patients who do have a condition. Also called "true positive rate". Also see *validity*.

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial (*ICH E6/R1*). The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). (*WHO*)

Sponsor-investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (*ICH E6/R1*)


Spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines: Medicines that are deliberately and fraudulently mislabelled with respect to identity and/or source. Use of SFFC medicines may result in treatment failure or even death. Increasing international trade of pharmaceuticals and sales via the internet has further facilitated the entry of counterfeit products into the supply chain. In 2006 this led to WHO's launch of the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). Also see *International Medical Products Anti-Counterfeiting Taskforce*. (*WHO*)

Stability: The ability of a product to retain its chemical, physical, microbiological and biological properties within specified limits throughout its shelf-life. (*WHO*)

Stability budget: A stability budget considers long term, accelerated, and stress temperature exposure, as well as temperature cycling studies to determine the amount of time out of storage that a drug product may experience without any significant risk to its quality (*PDA*). Temperature sensitive products may have limited time that they can be exposed to temperature outside label storage conditions and still meet quality attributes through expiry. The stability budget ensures product will meet shelf life specifications given end to end time out of storage requirements.

An example of a stability budget (for an imaginary product)

[Name of the product]



Product indications: [what is the product for]

[product image]

Recommended storage			+2 to +8°C (36 to 46°F)			
Recommended shipping			+2 to +8°C (36 to 46°F)			
Temperature and time supported outside recommended storage	Temperature range	Time duration				
		Manufacturer	Internal customer	Intermediate customers		End customer
		Distribution	Affiliate	Wholesaler/ Distributor/ Government	Pharmacy/ Physician/ Hospital	Patient
	-15 to +1°C (5 to 35°F)	2 days	1 day	1 day	1 day	1 day
	+2 to +8°C (36 to 46°F)	Until expiry				
	+9 to +25°C (47 to 77°F)	21 days	5 days	3 days	3 days	Per product label or 42 days
	+26 to +30°C (78 to 86°F)	2 days	1 day	2 days	2 days	1 day

Stability indicating methods: Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the API or FPP, and that are specific so that the content of the API, degradation products, and other components of interest can be accurately measured without interference. (WHO)

Stability indicating parameters: Parameters that are direct or indirect indicators of product efficacy or safety demonstrated in clinical trials. They are used to assess product suitability throughout the shelf-life. Determination of these parameters should result in quantitative values with a detectable rate of change. Qualitative parameters such as sterility could also be considered but cannot be included in the statistical analysis. (WHO)

Stability studies (stability testing): Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period (or shelf-life) of an API or the shelf-life of an FPP. (WHO)

Stability tests: A series of tests designed to obtain information on the stability of a product order to define its shelf-life and utilization period under specified packaging and storage conditions. (WHO)

Staging area: Zone(s) of a warehouse designated for the short-term storage of incoming goods waiting to be moved into long-term storage, and also for storing outgoing goods awaiting shipment. (WHO)

Stakeholder: A stakeholder is a person or an organization that can affect or be affected by a decision or an activity. Stakeholders also include those who have the perception that a decision or an activity can affect them. Originally it was defined in 1963 by Stanford research Institute as “those groups without whose support the organization would cease to exist”. ISO 31000 distinguishes between internal (primary) and external (secondary) stakeholders.

Standard deviation: The measure of the variability of a sample of observations around the mean.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results. (WHO)

Standby generator: An electrical backup system that operates automatically by sensing the power loss. When utility power returns, it switches off and returns to standby mode again. Most units run on diesel, natural gas or liquid propane gas. Standby generators should be run weekly for self-test in order to ensure proper response to outages.

Starting material: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials. (WHO)

Statute: Formal written laws enacted by the legislative authority. Statutes are also sometimes referred to as “legislation.” Some statutes provide detailed rules for addressing a particular issue. In other situations, a statute will simply set forth general principles, and the legislature will delegate the responsibility for working out the details to administrative agencies. This often is the case for issues that require a great deal of technical expertise, such as setting standards for good manufacturing practices for pharmaceutical products. Legislatures may also delegate responsibility to administrative agencies in order to avoid having to make difficult political choices. (WHO)

Stock card: A generic name for either an inventory control card or a batch card. (WHO)

Stock keeping records: Records kept on products in storage. Also see *transaction records* and *consumption records*.

Stock-keeping unit (SKU): In the field of inventory management, a code number, typically used as a machine-readable bar code, assigned to a single item of inventory. As part of a system for inventory control, the SKU represents the smallest unit of a product that can be sold from inventory, purchased, or added to inventory. Applied to wholesale, retail, or production operations, the SKU can assist in monitoring transactions, tracking customer spending patterns, controlling inventory and purchasing, and providing information about pricing, for example via its Universal Product Code (UPC). In the context of this Technical Supplement, and depending on the level in the supply chain, an SKU may be a complete pallet, a tertiary carton, a secondary carton or a primary container. (WHO)

Stock out: A condition under which there are not enough commodities on stock to meet demand. If you need to deliver 30 units and you have only 25, you are in a stock out situation. It does not necessarily mean that you have “zero” stock. However, zero stock is the “worst” case scenario of a stock out situation.

Storage conditions (of APIs): In general an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment. (WHO)

General case for storage conditions of APIs (WHO)

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH	12 months or 6 months
Intermediate ^b	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

^a Whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is determined by the climatic condition under which the API is intended to be stored. Testing at a more severe long-term condition can be an alternative to testing condition, i.e., 25°C/60% RH or 30°C/65% RH.

^b If 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is the long-term condition there is no intermediate condition.

Active pharmaceutical ingredients intended for storage in a refrigerator (WHO)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	12 months
Accelerated ^a	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH	6 months

^a Whether accelerated stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe longterm condition can be an alternative to storage testing at 25°C/60%RH or 30°C/65%RH.

Active pharmaceutical ingredients intended for storage in a freezer (WHO)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20°C ± 5 °C	12 months

Storage temperatures: Temperatures adjusted to keep products within their recommended temperature range during storage.

Storage unit temperature/humidity distribution: The range and pattern of temperatures and/or humidity within a temperature controlled storage unit during normal operation. (WHO)

Recommended vaccine storage temperatures (WHO)

	National (up to 6 months)	Subnational (up to 3 months)	District (up to 1 month)	Service (up to 1 month)
+8°C	Liquid Lyophil	Liquid Lyophil	Liquid Lyophil	Liquid Lyophil
+2°C			All OPVs	All OPVs
-15°C	Acceptable Lyophil	Acceptable Lyophil		
-25°C	All OPVs	All OPVs		

Lyophil Lyophilized vaccines: BCG Hib (freeze-dried) Japanese encephalitis (live attenuated) Measles Measles, mumps, rubella (MMR) Measles, rubella (MR) Meningococcal A	Rabies (freeze-dried) Rotavirus (freeze-dried) Varicella Yellow fever	Liquid Liquid vaccines: Cholera DT DTP DTP, HepB DTP, HepB, Hib HepA HepB	Hib (liquid) HPV IPV Influenza Meningococcal ACYW Pneumo conjugate vaccine (PCV) Rabies (liquid)	Rotavirus (liquid) Tetanus toxoid Td Typhoid PS
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Note: Diluents should never be frozen. If diluents are packaged with vaccine, the product should be stored at +2°C to +8°C.

Bundled lyophilized-liquid combination vaccines should never be frozen and should be stored at +2°C to +8°C.

Store ledger: A stock keeping record that keeps information about all lots of a product. Ledger format is less flexible tool for store manager, because it is easy to run out of space for an individual product. It is also hard to add new products. Individual inventory cards can be kept in ABC order, but pages cannot be alphabetized in a bound book. (WHO)

Stress testing: Studies performed to determine the impact of extreme environmental factors such as light and extreme temperature. These studies are not usually performed as part of a stability programme, but are used instead to establish protective packaging and container conditions, and to support exclusionary labelling. (WHO)

Stress testing (of the API): Studies undertaken to elucidate the intrinsic stability of API. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing. Stress testing of the API can help identify the likely degradation products, which, in turn, can help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The

nature of the stress testing will depend on the individual API and the type of FPP involved.

Stress testing may be carried out on a single batch of the API. It should include the effect of temperature (in 10°C increments (e.g., 50°C, 60°C, etc.) above the temperature used for accelerated testing), humidity (e.g., 75% relative humidity (RH) or greater) and, where appropriate, oxidation and photolysis on the API. The testing should also evaluate the susceptibility of the API to hydrolysis across a justified range of pH values when in solution or suspension. (*WHO*)

Stress testing (of the FPP): Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photostability testing and specific testing on certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products). (*WHO*)

Study product: See *investigational product*.

Study protocol: A document detailing the scope, objectives and operational specifics of a series of tests or data collection (study) written and approved in advance of execution of the study.

Sub-investigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). (*ICH E6/R1*) See also *investigator*.

Subject/trial subject: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control. (*ICH E6/R1*)

Summary report: A simple report that lists the name of the facility, reporting period, beginning quantity in hand, receipts, and quantities issued or dispensed, losses and adjustments, and ending quantity in hand for each product (usually monthly or quarterly).

A sample monthly summary report (WHO)

Reporting facility:		Reporting period:	
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Commodity name	Opening balance (doses)	Received (doses)	Issued (doses)	Losses/ adjustments (doses)	End balance (doses)	AMC	Stock level (months)
A	B	C	D	E	F	G	H
OPV							
DTP+HepB							
BCG							
BCG diluent							
Measles							
Measles diluent							
AD syringe BCG							
AD syringe (0.5 ml)							
Safety box							

Explanation of losses and adjustments:

Report by:

Preparation date:

Title:

Supercooling: The process of lowering the temperature of a liquid or gas below its freezing point without it becoming a solid. A liquid crossing its standard freezing point will crystalize in the presence of a seed crystal or nucleus around which a crystal structure can form creating a solid. Lacking any such nuclei, the liquid phase can be maintained all the way down to the temperature at which crystal homogeneous nucleation occurs.

The melting of a solid above the freezing point (the process opposite to supercooling) does not work since a solid will almost always melt at the same temperature for a given pressure. Because of this, “melting point” is identified in establishing scientific freezing point. This is often called “the principle of observing the disappearance rather than formation of ice”.

Superiority trial: A trial with the primary objective of showing that the response to the investigational product is superior to a comparative agent (active or placebo control). (*ICH E9*)

Supply chain: A system of organizations, people, activities, information, and resources involved in moving a product from the supplier to end user in a manner that ensures that the product arrives in good condition. (WHO)

Supporting stability data: Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers other than those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed retest period or the shelf-life and storage conditions. (WHO)

Surveillance: The continuing, systematic collection of data that is analyzed and disseminated to enable decision-making and action to protect the health of populations.

Surveillance aims to assess the magnitude of problem; monitoring implantation of health programmes; understanding local epidemiology of the problem; assessing changes in disease trends or its distribution in the community; identifying specific risk groups; and assessing the impact of the intervention programme on control of diseases.

The data-collection method determines the type of surveillance, so that:

- passive surveillance is based on passive reporting;
- sentinel surveillance is based on selected institutions or people;
- active surveillance is based on systematic search for cases.

Passive surveillance is the routine reporting of diseases from health care facilities. Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organised process. Examples of active surveillance are, cohort studies that have been conducted in the United States of America, the United Kingdom, Denmark and others, to evaluate the safety of vaccines, in which all outcomes for specified events are identified in a predefined cohort using clinical information databases. Using such systems it is possible to ascertain events in a population completely, and in an unbiased manner, which facilitates accurate assessment of any potential safety issues. (WHO)

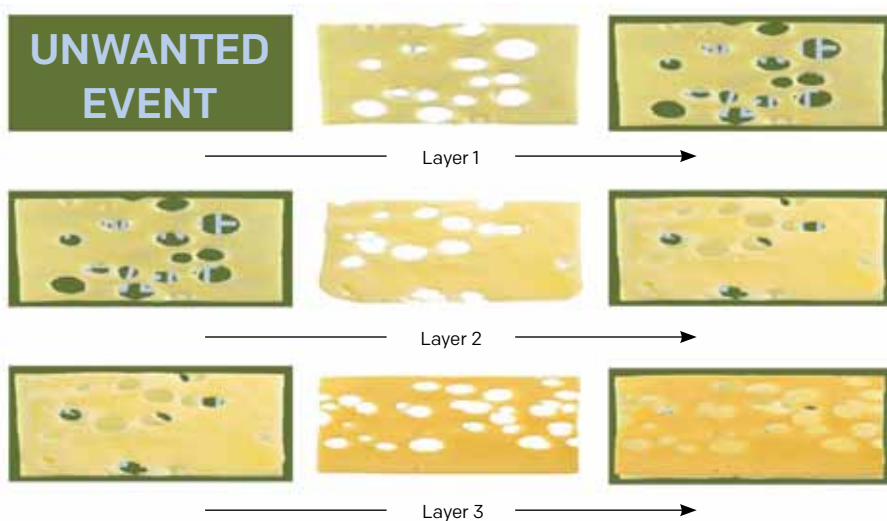
Suspect product: A TTSP whose presentation and/or pharmacological formulation indicates that it has not been manufactured by the company named on the packaging. A suspect product may show visible or pharmacological evidence of tampering. (WHO)

Suspected immunization error: Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action. (WHO)

Swiss cheese model: Redundant barriers intended to minimize risk of human errors as defined by Dante Orlandella and James T. Reason of the University of Manchester. It is widely used in aviation, engineering, healthcare, computer security and defence. The control measures (barriers) that are put in place intended to minimize the risk do not provide complete prevention, this is why redundant controls are necessary to minimize the risk. Like slices of Swiss cheese, the control measures also have holes in them. The system produces failures when a hole in each slice momentarily aligns, permitting (in JT Reason's words) "a trajectory of accident opportunity", so that a hazard passes through holes in all of the slices, leading to a failure.

The holes in the defences arise for two reasons: active failures and latent conditions. Nearly all adverse events involve a combination of these two sets of factors (*JT Reason*):

Swiss cheese model: Redundant controls helping to minimize the risk (Kartoglu)



Active failures are the unsafe acts committed by people who are in direct contact with the patient or system. They take a variety of forms: slips, lapses, fumbles, mistakes, and procedural violations. Active failures have a direct and usually short-lived impact on the integrity of the defences. At Chernobyl, for example, the operators wrongly violated plant procedures and switched off successive safety systems, thus creating the immediate trigger for the catastrophic explosion in the core. Followers of the person approach often look no further for the causes of an adverse event once they have identified these proximal unsafe acts. But, as discussed below, virtually all such acts have a causal history that extends back in time and up through the levels of the system.

Latent conditions are the inevitable “resident pathogens” within the system. They arise from decisions made by designers, builders, procedure writers, and top level management. Such decisions may be mistaken, but they need not be. All such strategic decisions have the potential for introducing pathogens into the system. Latent conditions have two kinds of adverse effect: they can translate into error provoking conditions within the local workplace (for example, time pressure, understaffing, inadequate equipment, fatigue, and inexperience) and they can create long-lasting holes or weaknesses in the defences (untrustworthy alarms and indicators, unworkable procedures, design and construction deficiencies, etc.). Latent conditions—as the term suggests—may lie dormant within the system for many years before they combine with active failures and local triggers to create an accident opportunity. Unlike active failures, whose specific forms are often hard to foresee, latent conditions can be identified and remedied before an adverse event occurs. Understanding this leads to proactive rather than reactive risk management.

To use another analogy: active failures are like mosquitoes. They can be swatted one by one, but they still keep coming. The best remedies are to create more effective defences and to drain the swamps in which they breed. The swamps, in this case, are the ever present latent conditions. (JT Reason)

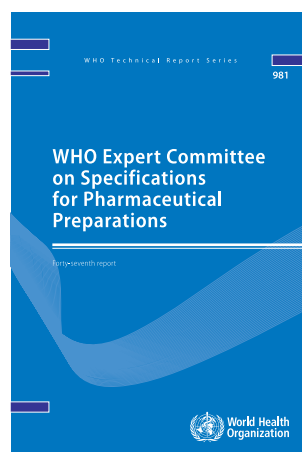
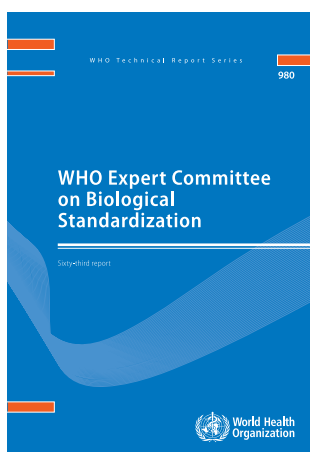
Systematic sampling: A type of random sampling where study units are arranged in some kind of sequence as in a directory or in a series of index cards and a predetermined fraction of the population is selected as the study sample. (WHO)



T_{max}: The amount of time that a drug is present at the maximum concentration in serum.

Technical agreement: *See service level agreement.*

Technical Report Series (TRS): A series publication by WHO on reports and recommendations including all adopted guidelines in the form of Annexes from WHO Expert Committees, endorsed by the WHO Executive Board.



ECBS and ECSPPP expert committees reports in Technical Report Series (WHO)

Temperature control device: A device which actively controls the operation of cooling plant used to store or transport TTSPPs. (WHO)

Temperature Control Regulations (TCR): A comprehensive guide published by the IATA, designed to enable stakeholders involved in the transport and handling of pharmaceutical product to safely meet the requirements. The TCR provides you access to the most current and efficient practices for your perishable cargo operations and an integral tool to achieve cost savings and avoiding delays by guaranteeing your shipments are problem-free and compliant with international or local regulations. The TCR includes:

- Up-to-date airline and government requirements pertaining to the transport of healthcare and pharmaceutical products
- Requirements on handling, marking & labeling
- Necessary packaging requirements
- Information on handling procedures
- The necessary documentation needed when transporting healthcare products

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits. (WHO)

Temperature excursion: An event in which a TTSP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data. In situations in which cool water-packs are used for vaccine transport, an excursion up to a maximum of +20°C is acceptable. (WHO)

Temperature-modified: Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits. (WHO)

Temperature monitoring: A process to ensure products remain within recommended temperature range during their storage and transport by using variety of devices and tools. It is essential that the temperature monitoring process is not purely mechanical. Personnel must be made responsible for their actions and must know how to react effectively to problems as soon as they arise. (WHO)

The table below shows the recommended temperature monitoring devices for the fixed storage locations in a typical vaccine supply chain.

Recommended temperature monitoring devices for vaccine supply chain (WHO)

	International transport	Primary vaccine store	In-country transport	Intermediate vaccine store	In-country transport	Service level
Electronic shipping indicators						
Vaccine cold chain monitor card						
Irreversible freeze Indicator						
Programmable electronic temperature monitoring system						
Portable thermometer						
User programmable temperature data loggers						
30-day electronic refrigerator temperature logger						
Vaccine vial monitor						

Recommended levels are indicated by shading

1. Vaccine cold chain monitor card is recommended only to accompany dry ice shipments.
2. Since electronic shipping indicators have the low freezing alarms, when they are in use there is no need to include a separate freeze indicator.
3. Portable thermometer is not considered as a monitoring device (except in freezers in small subnational stores); however, it can be used as a backup device in refrigerators.
4. User programmable temperature data loggers are recommended for study purposes, not for routine temperature monitoring.

**Recommended temperature monitoring devices for the fixed storage locations
in a typical vaccine supply chain (modified from WHO)**

Cold chain equipment	Temperature monitoring devices	
	Recommended devices	Minimum requirement
Freezer rooms in primary or sub-national stores	<ul style="list-style-type: none"> ■ Electronic continuous temperature monitoring system ■ External digital thermometer or gas/vapour pressure dial thermometer ■ Temperature alarm system with auto-dialer 	<ul style="list-style-type: none"> ■ External digital thermometer or gas/vapour pressure dial thermometer ■ Pen recording thermometer ■ Temperature alarm system
Cold rooms in primary or sub-national stores	<ul style="list-style-type: none"> ■ Electronic continuous temperature monitoring system ■ External digital thermometer or gas/vapour pressure dial thermometer ■ Temperature alarm system with auto-dialer 	<ul style="list-style-type: none"> ■ External digital thermometer or gas/vapour pressure dial thermometer ■ Pen recording thermometer ■ Temperature alarm system
Vaccine freezers in primary stores and large sub-national stores	<ul style="list-style-type: none"> ■ Electronic continuous temperature monitoring system ■ Temperature alarm system with auto-dialer 	<ul style="list-style-type: none"> ■ Alcohol stem thermometer **
Vaccine refrigerators in primary stores and large sub-national stores	<ul style="list-style-type: none"> ■ Electronic continuous temperature monitoring system ■ Temperature alarm system with auto-dialer ■ Electronic freeze indicators 	<ul style="list-style-type: none"> ■ Alcohol stem thermometer ** ■ 30-day electronic refrigerator temperature logger
Vaccine freezers in small sub-national stores	<ul style="list-style-type: none"> ■ Alcohol stem thermometer ** 	<ul style="list-style-type: none"> ■ Alcohol stem thermometer **
Vaccine refrigerators in small sub-national stores and health facilities	<ul style="list-style-type: none"> ■ 30-day electronic refrigerator temperature logger 	<ul style="list-style-type: none"> ■ Alcohol stem thermometer ** ■ Electronic freeze indicator

** Bi-metallic dial thermometers are not recommended because they quickly lose their calibration.

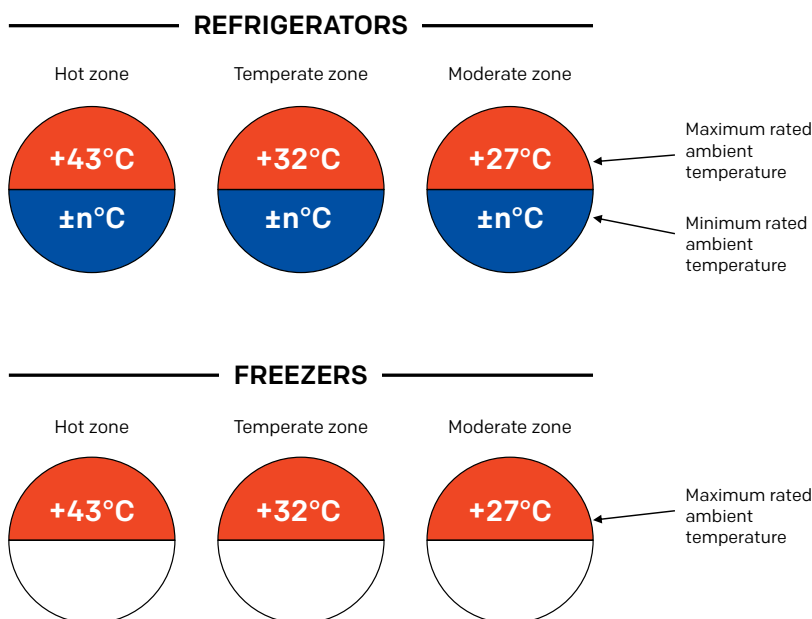
Temperature monitoring device: A device which monitors the temperature of spaces used to store or transport TTSPs. (WHO)

Temperature stabilizing medium: Ice or gel packs; gel bricks, bottles or pouches; cool water or warm water packs, phase change materials, dry ice, rapid evaporation media which limit exposure of packed product to excessively high or low temperatures during transport: also referred to as refrigerants or coolants. (WHO)

Temperature zone symbols for refrigerators: Circle shape signage indicating climate zones along with maximum and minimum rated temperatures for WHO PQS prequalified vaccine refrigerators and freezers.

For refrigerators, the upper semi-circle shows the maximum rated ambient temperature which if exposed to temperatures above this, the equipment will not maintain the vaccine at acceptable temperature range. The lower semi-circle shows the minimum rated ambient operating temperature that is established by PQS testing. If the equipment is exposed to temperatures below this figure, the vaccine will be at risk of freezing. The freezer symbols have a blank lower semi-circle because minimum rated ambient temperature is not relevant.

Temperature zone symbols for refrigerators (WHO)



Tertiary pack or carton: The pack or carton that contains a number of secondary cartons; usually constructed of corrugated fibreboard. The tertiary carton is not the same as the insulated shipper used for international air shipment of TTSPPs, although the insulated shipper may contain one or more of these cartons. (WHO)

Therapeutic equivalence: Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with re-

spect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. (WHO)

Thermal equilibrium: A state of no heat flow between two physical systems that are connected to each other through a path that is permeable to heat. Thermal equilibrium obeys the rules of zeroth law of thermodynamics. Thermal equilibrium also happens in one physical system when the temperature within the system is spatially and temporally uniform.

Thermal stability as lot release test: Stability of a vaccine after exposure to a temperature higher than that recommended for storage, for a specified period of time, often expressed in terms of change in potency. (WHO)

Thermal time constant: The most common definitions of the thermal reaction time are the so-called tau (τ , the 19th letter of the Greek alphabet) and "T90". Tau stands for the time a device needs to adapt to 63% of the end value of a temperature change whereas T90 represents the time to adapt to 90% of the change. T90 is approximately equal to 2.5 times Tau. These constants are commonly evaluated by experiment on the test device under well-defined conditions as described in EN 12830.

Thermistor: The term "thermistor" is used to describe an electronic component whose principle characteristic is a large change in electrical resistance with a change in its body temperature. The word "thermistor" is derived from the description "thermally sensitive resistor". Thermistors used for precision temperature measurement are generally "negative temperature co-efficient" (NTC) types. NTC thermistors are devices whose resistance decrease as their temperature increases. NTC

Thermistors offer many advantages in the area of temperature sensing: sensitivity (typically a -3% to -6% change in resistivity per a 1°C increase in temperature); small size, diverse configurations; and high accuracy. NTC Thermistors are manufactured from proprietary formulations of ceramic materials and transitional metal oxides (C Willis).



Thermocouple connected to a multimeter displaying room temperature (Sovxx, Wikipedia)

Thermocouple: Thermocouples are based on the change in the junction potential of two dissimilar metals as a function of temperature. Many metal pairs can be used, and each pair provides a unique range, accuracy, and precision. Precision and accuracy depend on the quality of the electronics used to measure the voltage across both metals and the type of temperature reference used. (USP 1118)

Thermolabile: Often used to describe biochemical substances which are subject to destruction/decomposition or change in response to heat.

Thermosensitivity: The state or condition of pharmaceutical/biological products being thermosensitive, showing reaction to heat. All vaccines are thermosensitive.

Vaccine sensitivity to heat (WHO)

Heat sensitivity	Vaccine
Most sensitive group	Oral poliovirus
	Varicella-zoster virus
	Influenza (inactive, split)
	Inactive poliovirus
	Japanese encephalitis (live)
	Measles, mumps, rubella
	Cholera (inactivated)
	DTaP
	DTwP
	DTap-hepatitis B-Hib-IPV (hexavalent)
	DTwP-hepatitis B-Hib (pentavalent)
	Hib (liquid)
	Measles
	Rotavirus (liquid and freeze dried)
	Rubella
	Yellow fever
	Bacillus Calmette-Guérin
	Human papillomavirus
	Japanese encephalitis (inactivated)
	TT, DT, Td
Least sensitive group	Hepatitis A
	Hepatitis B
	Hib (freeze dried)
	Meningitis A (polysaccharide-protein conjugate)
	Meningitis C (polysaccharide-protein conjugate)
	Pneumococcal (polysaccharide-protein conjugate)
	Rabies
	Typhoid polysaccharide

Note: Freeze-dried vaccines are in bold

Vaccine sensitivity to freezing (WHO)

	Vaccine
All these vaccines are damaged by freezing	DTaP
	DTaP-hepatitis B-Hib-IPV (hexavalent)
	DTwP
	DTwP-hepatitis B-Hib (pentavalent)
	Hepatitis A
	Hepatitis B
	Human papillomavirus
	Meningitis C (polysaccharide-protein conjugate)
	Pneumococcal (polysaccharide-protein conjugate)
	TT, DT, Td
These vaccines are not damaged by freezing	Cholera (inactivated)
	Influenza (inactivated, split)
	Hib (liquid)
	Inactivated poliovirus
	Typhoid polysaccharide
	Meningitis A (polysaccharide-protein conjugate)*
	Rotavirus (liquid and freeze dried)
	Yellow fever
	Bacillus Calmette-Guérin
	Hib (freeze dried)
	Japanese encephalitis (live and inactivated)
	Measles
	Measles, mumps, rubella
	Oral poliovirus
	Rabies
	Rubella
	Varicella-zoster virus

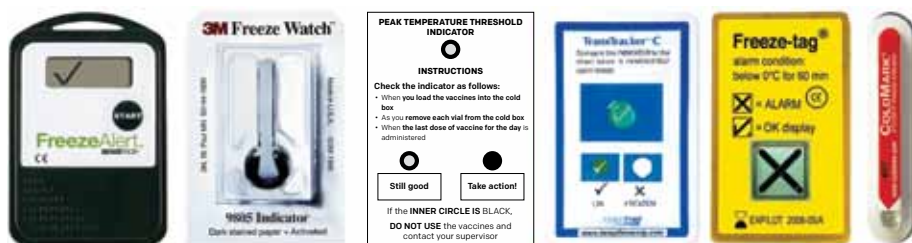
Note: Freeze-dried vaccines are in bold

* The diluent for meningitis A vaccine is damaged by freezing

Thermostability: The quality of a substance to resist irreversible change in its chemical or physical structure at a high relative temperature.

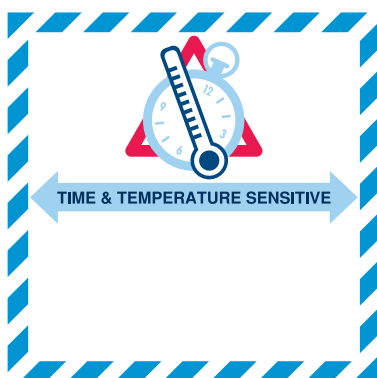
Third-party accreditation: Accreditation or certification by an organization that issues credentials or certifies third parties against official standards as a means of establishing that a contractor is competent to undertake a specific type of work. Third-party accreditation organizations are themselves formally accredited by accreditation bodies; hence they are sometimes known as *accredited certification bodies*. The accreditation process ensures that their certification practices are acceptable, typically meaning that they are competent to test and certify third parties, behave ethically and employ suitable quality assurance.

Threshold indicator: Indicators providing a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature. Also see *freeze indicator*.



Examples of threshold indicators

Time and temperature sensitive label (IATA): A mandatory label for the transportation of healthcare cargo shipments. It is issued by the IATA and recognized by the air cargo industry as a best practice, and is effective since July 1st, 2012.



Time and temperature sensitive label (IATA)

It is the responsibility of the shipper (or designated shipper's agent by service agreement) to ensure the label is applied properly for time and temperature sensitive healthcare cargo shipments booked as such. The lower half of the label must never be left blank and must indicate the external transportation temperature range of the shipment. The temperature range must only be shown in Celsius. No other temperature information must be indicated on the label except, when agreed between the parties it may be used to communicate the Standard Operating Procedures (SOP) number. The temperature range indicated on the label always reflects the temperature external (or ambient

temperature) to the package allowed during transportation and distribution and not the actual product (internal) temperature.

Time and temperature sensitive pharmaceutical product (TTSP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended. (*WHO*)

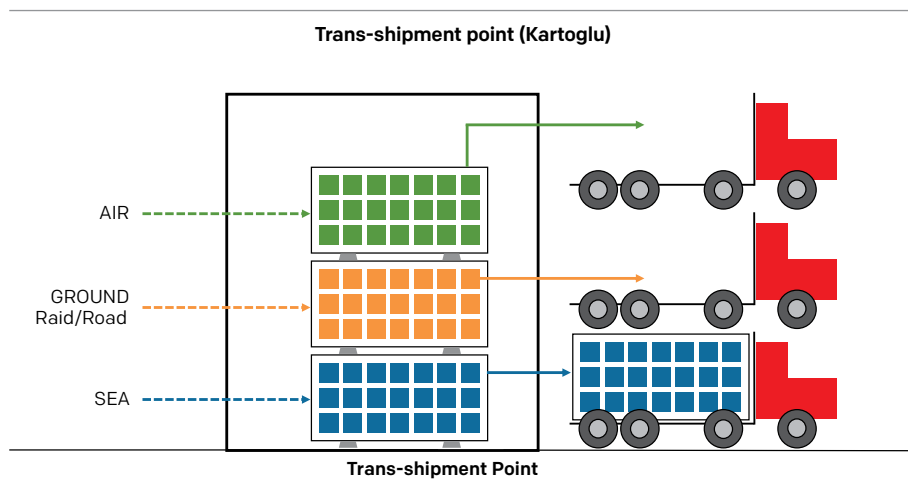
Time-temperature integrators (TTIs): Are generally chemically impregnated onto a pulp or paperboard substrate. Their reaction rate or diffusion process is used to estimate a temperature equivalent integrated over time. Thus, TTIs provide a measure of accumulated heat rather than instantaneous temperature such as a spike or critical threshold (see *chemical indicators*). The reactions are irreversible - once a color change, color development, or diffusion process has taken place, exposure to low temperatures will not restore the indicator to its original state. They change color, or are marked by a hue progression in intensity (generally from light to dark) in response to cumulative changes in temperature, such as heat, at a rate dependent on the Arrhenius equation. A TTI accumulates all of the temperature conditions experienced by the product to which it is affixed. The color development can be customized based on the known stability of the product, and in much the same way that most biologicals and pharmaceuticals degrade when exposed to heat - faster at higher temperatures, and slower at lower temperatures.

Traceability: The ability to identify and trace the history, distribution, location, and application of products, parts, materials, and services. A traceability system records and follows the trail as products, parts, materials, and services come from suppliers and are processed and ultimately distributed as final products and services. (*ISO 9000:2015*)

Transaction records: Records kept on products being moved from one facility to another. Also see *stock keeping records* and *consumption records*.

Transport temperature profile: Anticipated ambient temperature variation and duration to which a TTSP may be exposed during transport. (*WHO*)

Trans-shipment point: Similar to cross-dock centres in that orders for individual customers are picked at the central location, transported in bulk in large vehicles to the trans-shipment point where they are split into individual orders for individual customers for delivery in small vehicles. (*WHO*)



Treaties: International agreements in which governments agree to follow particular standards or procedures. Also known as “conventions”. Most treaties are not immediately legally binding, but rather become binding only when a country’s internal government formally adopts the agreement. Many human rights principles have been established through international treaties, including the International Covenant on Civil and Political Rights, the International Covenant on Economic, Social, and Cultural Rights, and numerous regional human rights conventions. Human rights treaties are significant because they require governments to promote human rights in both the public and private sectors. In some cases, treaty-based obligations can be enforced in domestic courts or in international tribunals. (*WHO*)

Trial site: The location(s) where trial-related activities are actually conducted.

Trial subject: An individual who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control (*WHO*). The individual may be:

- a healthy person who volunteers to participate in a trial;
- a person with a condition unrelated to the use of the investigational product;
- a person (usually a patient) whose condition is relevant to the use of the investigational product.

Triple point: The temperature and pressure at which a substance can exist in equilibrium in the liquid, solid, and gaseous states. The triple point of pure water is at 0.01°C and 4.58 mm of mercury and is used to calibrate thermometers.

TT2+ coverage indicator: Percent of women who receive two and more TT vaccine in relation to the overall infants under one year of age or live births. The numerator is an

aggregate of TT doses from the second dose onwards. The first dose is not included in the coverage indicator, but reported separately since it is not protective.

$$\text{TT2+ coverage} = \frac{\text{TT2} + \text{TT3} + \text{TT4} + \text{TT5}}{\text{Infants under 1 year of age or live births}} \times 100$$

Type I error: The statistical error (said to be “of the first kind” or alpha error) made in testing a hypothesis when it is concluded that a treatment or intervention is effective when it really is not. Type I error is sometimes referred to as a “false positive”.

Type I error

		“Gold standard” test		TOTAL
		Condition positive	Condition negative	
Test under validation	Test outcome positive	True positive (A)	False positive Type I error (B)	A + B
	Test outcome negative	False negative <i>Type II error</i> (C)	True negative (D)	C + D
TOTAL		A + C	B + D	A + B + C + D

$$\begin{aligned} \text{False Positive Rate} &= \frac{B}{B + D} = \frac{\text{Number of false positives}}{\text{Number of false positives} + \text{number of true negatives}} \\ (\text{Type I error}) \end{aligned}$$

Type II error: The statistical error (said to be “of the second kind” or beta error) made in testing a hypothesis when it is concluded that a treatment or intervention is not effective when it really is. Type II error is sometimes referred to as a “false negative”.

Type II error

		“Gold standard” test		TOTAL
		Condition positive	Condition negative	
Test under validation	Test outcome positive	True positive (A)	False positive Type I error (B)	A + B
	Test outcome negative	False negative Type II error (C)	True negative (D)	C + D
TOTAL		A + C	B + D	A + B + C + D

$$\begin{aligned} \text{False Negative Rate} &= \frac{C}{A + C} = \frac{\text{Number of false negatives}}{\text{Number of true positives} + \text{number of false negatives}} \\ (\text{Type II error}) \end{aligned}$$

Type-examination: Some products such as cold rooms and solar power systems are site-specific but are made up of standard manufactured components. These are pre-qualified by a “type-examination” procedure. A technical expert carries out a detailed assessment against a standard checklist to determine that all the components comply fully with the specification. Type-examination is also used for certain other product types which meet normal industry standards, and are not considered to be programme-critical; for example, temperature data loggers used for temperature monitoring studies.

Type-testing: A product that is programme-critical is generally “type-tested”. Type-testing also starts with a “type-examination” procedure. This is followed by standardized laboratory testing to ensure full compliance with the critical performance requirements.



ULD regulations: The ULD Regulations (ULDR) contains both technical and operational standard specifications and regulatory requirements as well as airlines requirements applicable to overall ULD operations. The creation of the IATA ULDR has involved extensive consultation and collaboration with all segments of the air cargo industry. The IATA ULDR replaces the former IATA ULD Technical Manual (UTM). The ULDR provides minimum standard specifications for designing and manufacturing ULDs that conform to IATA, ISO, SAE, and other national and international standards; essential and detailed guidelines for all aspects of ULD operations; training requirements and standards; and supporting material for airlines creating operations manuals containing ULD related content for use by their own or outside staff.

Uncertainty: Lack of certainty, a situation that involves imperfect and/or unknown information. Uncertainty is a state of having limited knowledge where it is not possible to exactly describe the existing state or more than one possible outcome. Risk and uncertainty are closely related, but slightly different concepts. They are both based on current lack of certainty in a potential fact, outcome or scenario and defined by probabilities and includes subjectivity since everything depends on how much we know about the fact, outcome or scenario.

M Mauboussin differentiates the uncertainty and risk with following definitions: Risk is when we don't know what is going to happen next, but we do know what the distribution looks like; and uncertainty is when we don't know what is going to happen next, and we do not know what the possible distribution looks like.

Uncertainty (of measurement): A parameter associated with the result of a measurement that characterises the dispersion of the values that could reasonably be attributed to the measurand. (*JCGM/GUM 1995*)

Undercooling: See *supercooling*.

Uniclass: Unified Classification for the Construction Industry, published in 1997 in the United Kingdom, is a classification scheme for the construction industry. It is intended for organizing library materials and for structuring product literature and construction project information.



Airbus A300 fuselage cross-section, showing the passenger compartment above and LD-3 cargo containers below. On display at the Deutsches Museum in Munich, Germany (Asiir/Wikipedia)

Unit load device (ULD): A container used for consolidating and transporting cargo aboard aircraft. They are generally made of aluminium and/or fibreglass and configured to fit the geometry of an aircraft and are considered part of the aircraft frame. Large active systems fall into the category of ULD. There are two basic sizes classified by the airline industry: LD-3 and LD-9.

Universal packaging solution: A shipping container whose proper performance does not require more than one packing configuration regardless of seasonal variants such as summer and winter or hot and cold exposure.

Uppsala Monitoring Centre (UMC): An independent foundation and a WHO Collaborating Centre for International Drug Monitoring and scientific research, located in Uppsala, Sweden. The first international drug monitoring centre was established by WHO after the thalidomide disaster, since 1978 the Programme has been carried out by UMC. The UMC works by collecting, assessing and communicating information from Member States national pharmacovigilance programmes in regard to the benefits, harm, effectiveness and risks of drugs and other substances used in medicine to improve patient therapy and public health worldwide. UMC is the custodian and manager of VigiBase, the WHO global database of more than 8 million reports of adverse reactions to medicines dating back to 1968. Its primary task is the collection, screening and analysis of reports of suspected adverse reactions to medicines and risks from over 100 member countries in the WHO Programme. Its primary purpose is the detection and communication of emerging concerns about threats to the safety of patients to support good decision-making for the safer and more effective use of medicines. UMC is the maintenance organization for WHO-ART (Adverse Re-



action Terminology) and the WHO Drug Dictionaries, with more than 1,000 customers worldwide. For details see <http://www.who-umc.org/>

User requirement specification (URS): The attributes assigned by the user in advance of a qualification test to establish minimum performance limits. Sometimes referred to as a *functional requirements document*. (WHO)

Utilization factor: The percentage of the total volume available for storing TTSPPs that can reliably be achieved in practice, taking account of the types of stock-keeping unit, the types of load support system and the stock management systems used in the store. (WHO)

Utilization period: A period of time during which a reconstituted preparation of the finished dosage form in an unopened multi-dose container can be used. (WHO)

V

Vaccination coverage: Percent of people who receive one or more vaccine(s) of interest in relation to the overall target population.

$$\text{Vaccination coverage} = \frac{\text{Number of infants under 1 year of age receiving all required doses for a selected vaccine during the past 12 months}}{\text{Target population of infants under 1 year of age or live births}} \times 100$$

Vaccination failure: Vaccination failure is based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Vaccination failure can be due to vaccine failure (either “primary” when immune response is inadequate or “secondary” when the immune response wanes) or failure to vaccinate (i.e., when an indicated vaccine was not administered appropriately for any reason). (WHO)

Vaccine Arrival Report (VAR): The vaccine arrival report is a means of monitoring international shipments of vaccines in order to ensure that shipping guidelines are followed and that vaccine quality is maintained by encouraging increased ownership of the procurement process by all the parties involved. UN procurement agencies (UNICEF country offices, UNICEF Supply Division, PAHO Revolving Fund) enforce issuance of VARs for each shipment and for each vaccine in the shipment. Recipient governments and procurement agencies are responsible for the report, and for taking appropriate action if problems are reported (e.g., follow-up with the manufacturer, forwarding agent, WHO). For details on how to fill in the VAR, see <http://goo.gl/Zjixz7>

Vaccine arrival report used by UNICEF

VACCINE ARRIVAL REPORT (VAR)¹

This report is to be filled in by authorized staff, ratified by the Store Manager or the EPI Manager, and forwarded to the procurement agency within three days of vaccine arrival. Use one report for each vaccine in the shipment.

COUNTRY	REPORT No.		Date of report
Place, date and time of inspection			
Name of cold store, date and time vaccines entered into cold store			

PART I — ADVANCE NOTICE

MAIN DOCUMENTS	Date received by consignee	Copy sent to (AWB)	Copy of packing list	Copy of invoice	Copy of release certificate
Pre-shipment					
Shipping notification	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>

List other documents (if requested)

PART II — FLIGHT ARRIVAL DETAILS

AWB Number	Report of destination	Flight No.	ETA as per notification	Actual time of arrival
			Date Time	Date Time

NAME OF CLEARING AGENT: _____ ON BEHALF OF: _____

PART III — DETAILS OF VACCINE SHIPMENT

Purchase Order No.	Consignee	Vaccine description (Type and description)	Manufacturer	Country
--------------------	-----------	--	--------------	---------

Vaccine				Diluent/droppers			
Lot Number	Number of boxes	Number of vials	Expiry date	Lot Number	Number of boxes	Number of units	Expiry date

(Continue on separate sheet if necessary)

Was quantity received as per shipping notification?	Yes <input type="checkbox"/> No <input type="checkbox"/>	Comments
If not, were details of short-shipment provided prior to vaccine arrival?	Yes <input type="checkbox"/> No <input type="checkbox"/>	

¹ Adapted from the Standard UNICEF Vaccine Arrival Report from WHO Guidelines on the international packaging and shipping of vaccines (WHO/M8/05.23)
No. = Number
WHO recommends all UN agencies, countries and non-governmental organizations procuring vaccines adopt this report.

Page 1

Report No. _____

PART IV — DOCUMENTS ACCOMPANYING THE SHIPMENT

Invoice	Packing list	Release certificate	Vaccine Arrival Report	Other
Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Comments				

PART V — STATUS OF SHIPPING INDICATORS

Total number of boxes inspected	
Coolant type:	Dry ice <input type="checkbox"/> Icepacks <input type="checkbox"/> No coolant <input type="checkbox"/>
Temperature monitors present	VVM <input type="checkbox"/> Cold-chain card <input type="checkbox"/> Electronic device <input type="checkbox"/> Type: _____

PROVIDE BELOW DETAILS OF STATUS ONLY WHEN PROBLEMS ARE OBSERVED (in addition fill in ALARM REPORTING FORM if there are any ALARMS in electronic devices)

Box Number	LOT NO	Alarm in electronic device				Cold-chain monitor				Date/time of inspection
		>+6°C	>+30°C	<-10°C	<-2.5°C	A	B	C	D	

(Continue on separate sheet if necessary)

PART VI — GENERAL CONDITIONS OF SHIPMENT

What was the condition of boxes on arrival?

Were necessary labels attached to shipping boxes?

Other comments including description of alarms in electronic devices (continue on separate sheet if necessary).

PART VII — NAME AND SIGNATURE

Authorized Inspection Supervisor	DATE	Central store or EPI Manager	DATE
----------------------------------	------	------------------------------	------

For Procurement Agency office use only

Date received by the office: _____ Contact person: _____

Page 2

Vaccine carrier: Thermally insulated box typically used to transport vaccines from health facilities with refrigeration to outreach sessions where refrigeration and ice is unavailable. They are typically carried by a single health worker travelling on foot or by other means, where the combined journey time and immunization activity lasts from a few hours to a whole day. (WHO)

Two types of vaccine carrier are described:

- **Short range:** With a minimum cold life of 15 hours.
- **Long range:** With a minimum cold life of 30 hours.

Long range vaccine carrier, PHD9 manufactured by SAVSU Technologies (WHO PQS code E004/039)



Vaccine cold box: Thermally insulated box typically used to maintain the cold chain when vaccines are transported in bulk from one fixed vaccine store to another. (WHO)

Two types of vaccine cold boxes are described:



Long range vaccine cold box, RCW25 manufactured by Dometic SARL (WHO PQS code E004/005)

- *Short range:* With a minimum cold life of 48 hours.
- *Long range:* With a minimum cold life of 96 hours.

Vaccine effectiveness: The protection rate conferred by vaccination in a specified population. Vaccine effectiveness measures both direct and indirect protection (i.e., protection of non-vaccinated persons by the vaccinated population). Vaccine effectiveness is also determined by vaccination coverage, correlation of vaccine strains with circulating strains and incidence of disease due to strains not included in the vaccine following introduction of the vaccine in that population. (WHO)

Vaccine (protective) efficacy: The reduction in the chance or odds of developing clinical disease after vaccination relative to the chance or odds when unvaccinated (WHO). Vaccine efficacy measures direct protection (i.e., protection induced by vaccination in the vaccinated population sample). Vaccine efficacy is calculated according to the following formula:

$$VE = \left(\frac{I_u - I_v}{I_u} \right) \times 100 \% = \left(1 - \frac{I_v}{I_u} \right) \times 100 \% = (1 - RR) \times 100 \%$$

Where:

I_u = incidence in unvaccinated population;

I_v = incidence in vaccinated population;

RR = relative risk

Vaccine Presentation and Packaging Advisory Group (VPPAG): The VPPAG was initially set up by GAVI, the Vaccine Alliance (formerly known as the Global Alliance for Vaccines and Immunization), in 2007 to respond to specific industry requests for technical advice concerning rotavirus and pneumococcal vaccines. For the latter, VPPAG's work fed into the World Health Organization's (WHO) target product profile (TPP) for pneumococcal vaccines to be eligible for Advance Market Commitment (AMC) financing. VPPAG also responded to a request from industry to provide guidance on rotavirus vaccines, primarily around reducing the package volume of existing products to ease cold chain burden for resource-constrained countries. Following a successful dialogue with one company, it was possible to fruitfully engage another in a similar exercise. In 2008, WHO took over the role of convening VPPAG, and the work of the group was broadened. By 2009, VPPAG had developed a draft generic preferred product profile (gPPP) to address the range of potential new vaccines in the development pipeline. With the establishment of WHO's Immunization Practices Advisory Committee (IPAC) in 2010, VPPAG also became a standing committee of IPAC, tasked with looking into specific issues aligned to its

expertise and helping to inform IPAC's policy recommendations that have implications for vaccine products.

Vaccine product: All components of a given vaccine formulation, including the immunogen (part of the vaccine that stimulates an immune response) and others that may be present such as the adjuvant, preservative and other additives used during the manufacturing process to confirm product quality/stability (e.g., potassium or sodium salts, albumin, gelatin), support growth and purification of specific immunogens (e.g., egg or yeast proteins, antibiotic) or inactivate toxins (e.g., formaldehyde). (WHO)

Vaccine product related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g., adjuvant, preservative or stabilizer). (WHO)

Vaccine quality defect-related reaction: An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device, as provided by the manufacturer. (WHO)

Vaccine storage capacity: For a freezer, refrigerator, cold box or vaccine carrier: the actual volume available for the storage of vaccine as stated by the equipment manufacturer or established by physical measurement. (WHO)

Vaccine usage rate: Proportion of vaccine issued which is administered, expressed in formula as follows:

$$\text{Vaccine usage} = \frac{\text{Number of doses administered}}{\text{Number of doses issued}} \times 100$$

Vaccine vial monitor (VVM): A label containing a heat-sensitive material which is placed on a vaccine vial to register cumulative heat exposure over time. The combined effects of time and temperature cause the inner square of the vaccine vial monitor to darken gradually and irreversibly. A direct relationship exists between the rate of color change and temperature: the lower the temperature, the slower the color change; the higher the temperature, the faster the color change. VVM is the only tool among all time temperature indicators that is available at any time in the process of distribution and at the time a vaccine is administered indicating whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged.

———— Cumulative heat exposure —————→



The principle purpose of the vaccine vial monitor (VVM) is to warn health workers when the cumulative heat exposure of a vial of vaccine has exceeded a pre-set limit, beyond which the vaccine should not be used. This is defined as the end point. Before the end point is reached, changes in the appearance of the VVM are used to alert health workers to the fact that heat exposure has occurred. Heat exposed vials can then be used in preference to those that have not been exposed. VVM is not a potency indicator. Therefore it does not directly measure vaccine potency, but gives information about the main factor that affects potency: heat exposure over a period of time.

VVM reaction rates are specific to four different models of VVM, relating to four groups of vaccines according to their stability at least at two specific temperature points. Vaccine manufacturers conduct stability studies at 5°C as well as at accelerated temperatures (25°C and 37°C) to provide data for best VVM category match. Although VVM can be custom made for each product, categorization approach of stability data have shown to work well, otherwise, cost of VVM would increase.

VVM performance specification and independent type-testing protocol are defined by WHO PQS protocols.

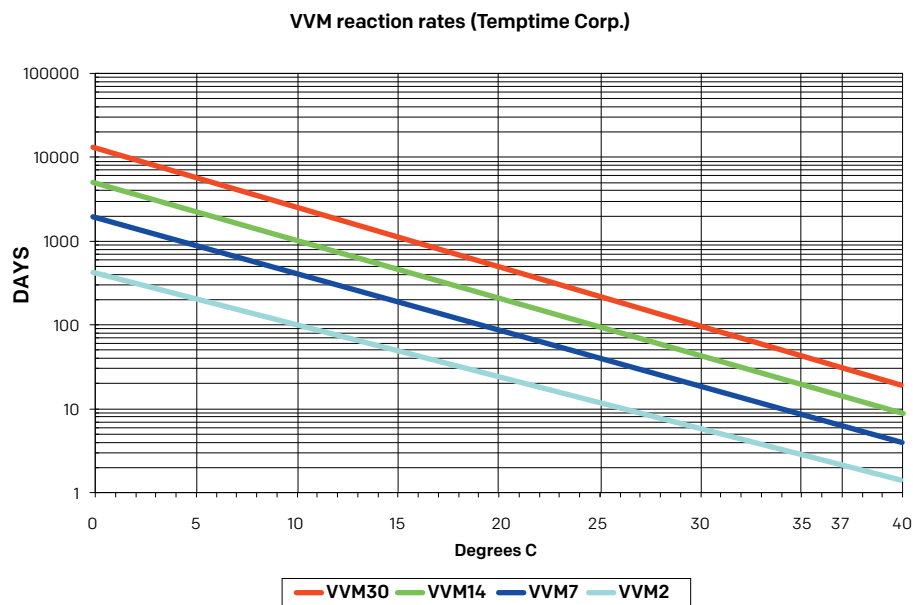
In their latest joint statement (2007) on the future of VVM, WHO and UNICEF urge Member States to include VVMs in all tender documents as well as urge donors to adopt a donation policy for inclusion of VVMs in all vaccine donations. WHO and UNICEF recommend all Member States to adopt VVM-based vaccine management policies to maximize benefits of VVM to:

- Ensure that vaccines administered have not been damaged by heat;
- Reduce vaccine wastage;
- Facilitate immunization outreach and increasing access and coverage;
- Pinpoint cold chain problems;
- Manage vaccine stocks and dispatch; and
- Prevent inadvertent freezing of vaccines.

VVM reaction rates by category of heat stability (WHO)

Category (Vaccines)	No. of days to end point at +37°C	No. of days to end point at +25°C	Time to end point at +5°C
VVM 30: High Stability	30	193	> 4 years
VVM 14: Medium Stability	14	90	> 3 years
VVM 7: Moderate Stability	7	45	> 2 years
VVM 2: Least Stable	2	N/A*	225 days

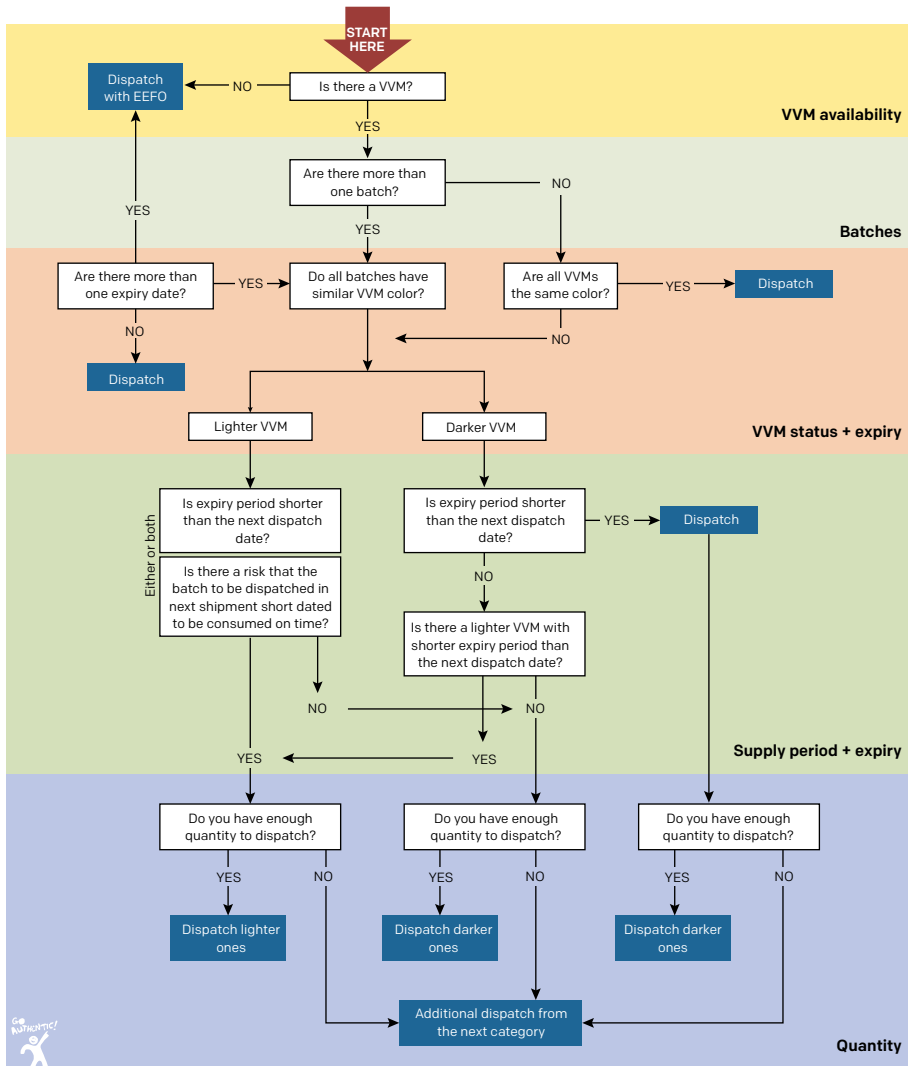
**VVM (Arrhenius) reaction rates determined at two temperature points*



WHO and UNICEF also recommend all Member States to consider adoption of policies permitting the use of vaccines beyond the cold chain where warranted for routine immunization activities or on a limited basis or under special circumstances, such as:

- National immunization days;
- Hard-to-reach geographical areas;
- Immunizations provided in the home – including hepatitis B vaccine birth dose;
- Cool seasons;
- Storage and transportation of freeze-sensitive vaccines where the risk of freezing is greater than the risk of heat exposure.

Using VVMs for dispatching vaccines (Kartoglu/EPELA)



Vaccine wastage factor: Factor indicating how much additional vaccine should be ordered in order to allow for the given wastage rate. It is used in vaccine forecasting.

$$\text{Vaccine wastage factor} = \frac{100}{100 - \text{Vaccine wastage rate}}$$

Since $[100 - \text{vaccine wastage rate}]$ equals the vaccine usage rate, the formula can also be written as:

$$\text{Vaccine wastage factor} = \frac{100}{\text{Vaccine usage rate}}$$

In a situation where vaccine wastage is 29%, 1.4 times more vaccine should be ordered so as to cover the estimated 29% vaccine wastage.

Vaccine wastage rates calculated from vaccine store records and service points cannot be combined since they measure and mean different things (note that the denominators of the two formulas are not the same). However, when it comes to incorporating vaccine wastage rate in estimates of national vaccine needs, both rates calculated at service level and at the storage facilities should be taken into account. National vaccine wastage rate can be calculated as follows:

$$\text{National vaccine wastage factor} = \frac{\text{Wastage factor of proportional vaccine wastage rate in unopened vials calculated from stores}}{\text{Wastage factor of vaccine wastage rate calculated from service points}} \times$$

For example, if the proportional vaccine wastage rate from vaccine stores is calculated to be 5% and the vaccine wastage rate from service points is 29%, the first requirement is for these to be converted into wastage factors.

$$\text{Vaccine wastage factor of proportional vaccine wastage rate in unopened vials from stores} = \frac{100}{100 - 5} = 1.05$$

$$\text{Vaccine wastage factor of vaccine wastage rate from service points} = \frac{100}{100 - 29} = 1.40$$

In this case the wastage factor to be included in the formula is $1.05 \times 1.40 = 1.47$

This means 1.47 times more vaccine should be ordered so as to cover the estimated nationwide vaccine wastage. If the wastage from storage facilities is not included in this calculation, only 1.4 times more vaccine would have been ordered instead of 1.47 times. This may result in vaccine shortage in the country.

The wastage rates cannot be merged. If they were, the total wastage rate would be $5\% + 29\% = 34\%$, giving a wastage factor of 1.51, whereas the above formula only gives a wastage factor of 1.47.

Vaccine wastage rate: Proportion of vaccine issued which is wasted (opposite of *vaccine usage*). Vaccine wastage happens both in opened and unopened vials. The below table summarizes the reasons for vaccine wastage:

Types of vaccine wastage (Kartoglu)

Vaccine wastage in unopened vials	Vaccine wastage in opened vials
<ul style="list-style-type: none"> ■ Expiry ■ VVM indication ■ Heat exposure ■ Freezing ■ Breakage ■ Missing inventory ■ Theft ■ Discarding vials returned from an outreach session 	<p>In addition to the types listed in the left column:</p> <ul style="list-style-type: none"> ■ Discarding remaining doses at the end of the session ■ Not being able to draw the number of doses indicated on the label of a vial ■ Poor reconstitution practices ■ Submergence of opened vials in water ■ Suspected contamination ■ Patient reaction requiring more than one dose

In vaccine stores, vaccine wastage occurs only in unopened vials because vaccine stores do not deliver any immunization. However, in all immunization points where immunization takes place, vaccine wastage happens both in opened and unopened vials. Therefore, vaccine wastage calculation should include both types of wastage.

Calculation of vaccine usage can be the first step in wastage calculations. Vaccine usage is defined as proportion of vaccine issued which is administered:

$$\text{Vaccine usage} = \frac{\text{Number of doses administered}}{\text{Number of doses issued}} \times 100$$

In this formula, “number of doses issued” includes doses used for immunization and all doses discarded or lost for any reason (including expiry, VVM indication, cold chain failure, freezing, missing inventory or routine discard of open vials of vaccine at the end of a session). Therefore, number of doses issued can be replaced with the following formula:

$$\text{Number of doses issued} = \text{Start balance at the beginning of the period} + \text{Number of doses received during the period} - \text{End balance at the end of the period}$$

This equation which is the denominator in the formula above includes all discards in opened and unopened vials.

Vaccine wastage is the opposite of vaccine usage and is given by:

$$\text{Vaccine wastage rate} = 100 - \text{vaccine usage rate}$$

Vaccine wastage rate (in storage facilities): Because vaccine stores handle only unopened vials the above formula cannot be applied to primary and intermediate vaccine stores. For years, an erroneous practice was used to calculate vaccine wastage rates by simply using primary store figures and the number of children immunized nationwide. The best vaccine wastage indicator for vaccine stores is the pro-

portional vaccine wastage in unopened vials. This can easily be calculated as follows.

$$\text{Proportional vaccine wastage rate in unopened vials in storage facilities} = \frac{\text{Doses discarded unopened}}{\text{Start balance} + \text{Number of doses received}} \times 100$$

The number of doses discarded includes all discards of unopened vials because of expiry, VVM indication, heat exposure, breakage, freezing, missing inventory and theft. This rate, which is specific for vaccine stores, should not be used for comparison with the vaccine wastage rate explained above. It gives the management performance levels of vaccine stores, since these only handle unopened vaccine vials. Because this category of wastage can be minimized the question arises as to what is the acceptable level for such failures.

Vaccines delivered during the calculation period should not be subtracted from the denominator because, if any quantities of vaccine are damaged during transportation, this wastage is recorded in the sender's vaccine store account.

Vaccines: A heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective host immunity against infectious disease.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria. (*PDA*)

Validity (of a diagnostic test): The extent to which a test measures what it is supposed to measure; in other words, it is the accuracy of the test. Validity is measured by sensitivity and specificity. Besides sensitivity and specificity, additional rates can be calculated to explain the strength of the test under validation.

Validity rates calculations

		"Gold standard" test		TOTAL
		Condition positive	Condition negative	
Test under validation	Test outcome positive	True positive (A)	False positive <i>Type I error</i> (B)	A + B
	Test outcome negative	False negative <i>Type II error</i> (C)	True negative (D)	C + D
	TOTAL	A + C	B + D	A + B + C + D

$$\begin{aligned}
 \text{Sensitivity} &= \frac{A}{A + C} = \frac{\text{Number of true positives}}{\text{Number of true positives} + \text{number of false negatives}} \\
 \text{Specificity} &= \frac{D}{B + D} = \frac{\text{Number of true negatives}}{\text{Number of true negatives} + \text{number of false positives}} \\
 \text{Positive Predictive Value} &= \frac{A}{A + B} = \frac{\text{Number of true positives}}{\text{Number of true positives} + \text{number of false positives}} \\
 \text{Negative Predictive Value} &= \frac{D}{C + D} = \frac{\text{Number of true negatives}}{\text{Number of false negatives} + \text{number of true negatives}} \\
 \text{False Discovery Rate} &= \frac{B}{A + B} = \frac{\text{Number of false positives}}{\text{Number of true positives} + \text{number of false positives}} \\
 \text{False Omission Rate} &= \frac{C}{C + D} = \frac{\text{Number of false negatives}}{\text{Number of false negatives} + \text{number of true negatives}} \\
 \text{False Negative Rate} &= \frac{C}{A + C} = \frac{\text{Number of false negatives}}{\text{Number of true positives} + \text{number of false negatives}} \\
 \text{False Positive Rate} &= \frac{B}{B + D} = \frac{\text{Number of false positives}}{\text{Number of false positives} + \text{number of true negatives}} \\
 \text{Positive Likelihood Ratio} &= \frac{\text{Sensitivity}}{\text{False positive rate}} = \frac{\text{Sensitivity}}{1 - \text{Specificity}} \\
 \text{Negative Likelihood Ratio} &= \frac{\text{False negative rate}}{\text{Specificity}} = \frac{1 - \text{Sensitivity}}{\text{Specificity}} \\
 \text{Diagnostic odds ratio} &= \frac{\text{Positive likelihood ratio}}{\text{Negative likelihood ratio}} \\
 \text{Accuracy (validity)} &= \frac{A + D}{A + B + C + D} = \frac{\text{Number of true positives} + \text{Number of true negatives}}{\Sigma \text{ total population}}
 \end{aligned}$$

VEN analysis: Method for categorizing stock as vital (V), essential (E), or nonessential (N). This system is sometimes modified to two categories – V and N. VEN analysis is often used to prioritize procurement when not enough funds exist to purchase all items requested. The system can also help determine which items should be kept in stock and which can be ordered when needed. (*WHO*) See also *ABC analysis*.

Vented shipping box: A container used to house an EDLM in order to record ambient air temperatures during transport, designed and constructed to maximize the airflow between the outside and inside of the container during the transport period. The container may be an integral part of a product shipment. Alternatively, if shipped separately, its overall size and weight should be similar to the container(s) used for the product(s) which are being monitored – this will ensure that the same handling practices are used. (WHO)



A vacuum insulation panel
(diepre, Shutterstock)

VIP: Vacuum insulation panels - A form of thermal insulation consisting of a nearly gas-tight enclosure surrounding a rigid core, from which the air has been evacuated. VIPs are made from nano-porous silica in a barrier film material formed under vacuum. The thermal resistance of evacuated insulation is a factor of five to ten better than conventional insulation of the same thickness.

Virus: Intracellularly replicating infectious agents that are potentially pathogenic, possessing only a single type of nucleic acid (either RNA or DNA), are unable to grow and undergo binary fission, and multiply in the form of their genetic material. (ICH Q5A/R1)

Volume per dose: The factor of volume of the secondary packaging over total number of doses of any product included in the secondary packaging. Volume per dose is an important factor for estimating required storage volume for the goods. For example, the below table provides a comparison of volume per dose for a HepB vaccine product from the same manufacturer in different vial sizes and secondary packaging:

Volume per dose variation of Hep B vaccine in various presentations and secondary packaging (WHO)		
Presentation	Number of vials in a secondary package	Volume per dose (cm ³)
1 dose vial	10	14.4
2 dose vial	10	7.2
6 dose vial	10	4.66
10 dose vial	10	3.22
10 dose vial	50	2.8

WHO issues maximum allowable volume per dose for each type of vaccine, and requires vaccine manufacturers to ensure that the storage volume per dose of the vaccines they supply to UN agencies remains below the maximum figures listed in below Table, and notify WHO if this is not attainable:

Maximum recommended packed volume* per vaccine dose, WHO

Vaccine type	Dose per vial	Maximum recommended dose per vial (cm ³)
BCG (freeze-dried)	20	1.2
DTP, DT, Td, TT	10	3.0
	20	2.0
DTP-HepB	2	6.0
	10	3.0
DTP-Hib	10	2.5
DTP+Hib (freeze-dried)	1	45.0
	10	12.0
DTP-HepB+Hib (freeze-dried)	1	22.0
	2	11.0
HepB	1	18.0
	1 in UNIJECT	20.0
	2	13.0
	6	4.5
	10	4.0
	20	3.0
Hib (liquid)	1	15.0
	10	2.5
Hib (freeze-dried)	1	13.0
	2	6.0
	10	2.5
Measles (freeze-dried)	10	3.5
MMR (freeze-dried)	1	16.0
	10	3.0
MR (freeze-dried)	10	2.5
Meningitis A&C	20	2.5
	50	1.5
OPV	10	2.0
	20	1.5
TT in UNIJECT	1	25.0
Yellow fever	5	6.5
	10	2.5
	20	1.0

**Packed volume includes the vaccine vial, the packet containing the vaccine vial, and any intermediate packaging (secondary packaging).*

WHO also issues maximum volume recommended for diluents and droppers.

Maximum recommended packed volume for diluents and droppers (WHO)

Vaccine type	Dose per vial	Maximum recommended dose per vial cm ³
Diluent for BCG	20	0.70
Diluent for Hib	1	35.0
	10	3.0
Diluent for Measles, MR, MMR	1	20.0
	10	4.0
Diluent for meningitis A&C	20	2.5
	50	1.5
Diluent for yellow fever	5	7.0
	10	6.0
	20	3.0
OPV droppers	n/a	17.0 (per unit)

Countries should use packed volume-per-dose to calculate cold-chain requirements if vaccines are to be kept in the cold chain in their secondary packaging. Storing vaccines in the shipping containers greatly increases the volume of cold storage needed, hence involves extra cost. However, this extra cost may be justifiable at higher-level stores where vaccine is kept alongside other refrigerated pharmaceuticals. In very large cold stores, where goods are stored and moved on pallets, vaccine should be stocked in their insulated shipping containers.

Vulnerable subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent. (*ICH E6/R1*)

W

Warm life test: The empty passive container is stabilized at +18.0°C and loaded with *warm water-packs*, which have been stabilized at the same temperature for a minimum of 24 hours. *Warm life* is measured from the moment when the container is closed, until the temperature of the coldest point inside the storage compartment first reaches 0.0°C at a constant ambient temperature of -20.0°C. (WHO)

Warm water-pack: A water-pack typically stabilized at room temperature, up to a recommended maximum of +24.0°C. Warm-packs are used for the transport of freeze-sensitive vaccines when the ambient temperature is below 0.0°C. (WHO)

Water-pack: Flat plastic container, filled with water, which can be used as a frozen water-pack (ice-pack), a cool water-pack or a warm water-pack. (WHO)

Water-pack freezing capacity (kg/24 hrs): The maximum weight of water-packs which can be fully frozen, in one batch, during a 24 hour freezing cycle. During this period the temperature of the vaccine storage compartment must remain within the acceptable temperature range of +2°C to +8°C. (WHO)



A water-pack (Kartoglu)

Well-being (of the trial subjects): The physical and mental integrity of the subjects participating in a clinical trial. (ICH E6/R1)

Well-established medicines: APIs (not products) which:

- have been marketed for at least five years in countries that undertake active post marketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar indications as in those countries. (WHO)

See also *well-established medicines combinations* and *well-established medicinal products*.

Well-established medicines combinations: Combinations of medicines which:

- have been marketed for at least five years in countries which undertake active post marketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar indications as in those countries. (WHO)

See also *well-established medicines* and *well-established medicinal products*.

Well-established medicinal products: Pharmaceutical products which contain well established medicines, and which:

- have been marketed for at least five years in countries that undertake active post-marketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar indications as in those countries. (WHO)

See also *well-established medicines* and *well-established medicines combinations*.

Work instruction: Describes *how* to complete a specific task. Contrast with an SOP which describes *who* (title or department) should carry out a series of tasks, and in what sequence. (WHO)

Working stock: Part of inventory available for normal demand in a given period. Usually safety stock is excluded from the working stock. In a typical supply chain, service level facilities such as hospitals and health centres; and retail pharmacies hold a working stock and administer product directly to patient or dispense products directly to the customers (retail pharmacies). Also called cycle stock or lot size stock. (WHO)

World Medical Association (WMA): An international organization representing physicians. It was founded on 17 September 1947, when physicians from 27 different countries met at the First General Assembly of the WMA in Paris. The organization was created to ensure the independence of physicians, and to work for the highest possible standards of ethical behaviour and care by physicians, at all times. This was particularly important to physicians after the Second World War, and therefore the WMA has always been an independent confederation of free professional associations. Funding has been by the annual contributions of its members, which has now grown to 111 National Medical Associations.



The WMA provides a forum for its member associations to communicate freely, to co-operate actively, to achieve consensus on high standards of medical ethics and professional competence, and to promote the professional freedom of physicians worldwide.

As an organization promoting the highest possible standards of medical ethics, the WMA provides ethical guidance to physicians through its Declarations, Resolutions and Statements. These also help to guide National Medical Associations, governments and international organizations throughout the world. The Declarations, Resolutions and Statements cover a wide range of subjects, including an International Code of Medical Ethics, the rights of patients, research on human subjects, care of the sick and wounded in times of armed conflict, torture of prisoners, the use and abuse of drugs, family planning and pollution.

For further details on WMA please visit <http://www.wma.net/en/index.html>

X

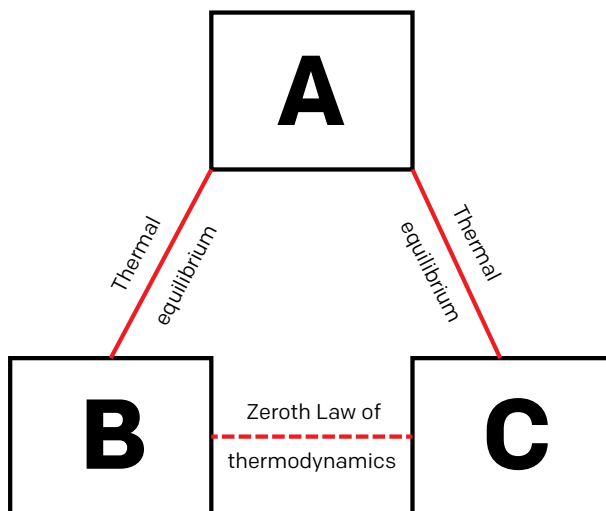
XPS: Extruded Polystyrene - XPS foam begins with solid polystyrene crystals. The crystals, along with special additives and a blowing agent, are fed into an extruder. Within the extruder the mixture is combined and melted under controlled conditions of high temperature and pressure into a viscous plastic fluid. The hot, thick liquid is then forced in a continuous process through a die. As it emerges from the die it expands to foam, is shaped, cooled, and trimmed to dimension. XPS resistance to heat flow (R-value) is around 4 for every 3 cm thickness of material. XPS boxes are cleanable, reusable and recyclable. XPS is non-toxic and chemically inert (fungi and bacteria cannot live on it).



XPS puzzle based insulated shipping container (Mediline Isothermal Solutions)

Zeroth law of thermodynamics: The law that if two thermodynamic systems are each in thermal equilibrium with a third, then they are in thermal equilibrium with each other. Originally defined by Ralph Howler and Edward Guggenheim as *"If two assemblies are each in thermal equilibrium with a third assembly, they are in thermal equilibrium with each other"*.

Zeroth Law of Thermodynamics (Kartoglu)



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Recommended videos

A year in the life of a vaccine
by Kevin O'Donnell
<https://vimeo.com/58148553>
running time 07:50 min (2012)



Kevin O'Donnell reviews the role of VVM and how it can be the answer to increase access and ensure quality of vaccine was not compromised due to unacceptable heat exposure.

Cold chain challenges
everywhere
by Simona Zipursky
<https://vimeo.com/58148554>
running time 03:48 min (2012)



Simona Zipursky reviews the cold chain challenges to demonstrate that problems are both in developing and industrialized countries and questions whether VVM should also be the answer for both.



Controlled temperature chain
(CTC): Delivering vaccines more
easily (episode 1 of 3)
by World Health Organization

https://www.youtube.com/watch?v=_wnt_3fkxBo&feature=youtu.be
running time: 05:28 min (2015)

The Controlled Temperature Chain, CTC, is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen.



Controlled temperature chain
(CTC): Implementing in the field
(episode 2 of 3)
by World Health Organization

<https://www.youtube.com/watch?v=dLq8q0mOquk&feature=youtu.be>
running time: 05:30 min (2015)

The Controlled Temperature Chain, CTC, is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen.



Controlled temperature chain
(CTC): Future development
(episode 3 of 3)
by World Health Organization

https://www.youtube.com/watch?v=e_5NZnik0sk&feature=youtu.be

running time: 04:37 min (2015)

The Controlled Temperature Chain, CTC, is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen.

Documents, records and record management

by James Vesper

<https://vimeo.com/51442647>

running time: 10'43 min (2011)



James Vesper reviews the critical aspects of documents, records and record management. Documents like procedures, protocols, methods, and specifications provide instructions so people can perform tasks and make decisions safely, effectively, compliantly, and consistently. Records, such as batch manufacturing records, cleaning logs, and laboratory data sheets and notebooks provide evidence that actions were taken and decisions were (hopefully) made in keeping with procedures and GMP expectations. Reports, another type of documentation, provide specific information on a particular topic (like an investigation or one aspect of product development) in a formal, standardized way.

Exploitation of stability data to reach the unreachable

by Umit Kartoglu

<https://vimeo.com/51442650>

running time: 10:53 min (2011)



Umit Kartoglu presents the critical aspect of exploitation of stability data to reach the unreachable through overview of studies taking vaccines beyond the 8 deg C all published in peer-review journals as well as a new concept of cool water packs by the WHO and Vaccine Vial Monitors. As he indicates that vaccines have become more stable and there is a clear prospect of increased or even complete heat stability, and concludes that in these circumstances the dogmatic approach to the cold chain causes resources to be wasted and places unnecessary restrictions on field operations.



Five senses:
Vaccine Vial Monitors
by World Health Organization
<https://vimeo.com/51505939>
running time: 20:46 min (2007)

A movie, produced for the 10th year anniversary of the introduction of vaccine vial monitors (VVM). The movie focuses on how this simple tool expands the horizon of the immunization programme and empowers health workers serving people at the very periphery of the health system. The theme and the goal are specific but there are scenes, human conditions, and different livings for everybody to see and think about them. Shot in Niger, Vietnam and Indonesia in 2007.



Global Perspectives in
Regulatory Oversight
by Rafik Bishara
<https://vimeo.com/51441317>
running time: 07:30 min (2011)

Members of the pharmaceutical supply chain have various global requirements to meet during the storage, transport and handling of time and temperature-sensitive products. Changing product portfolios, requirements for good storage and distribution practices, regulatory expectations, quality management, and risk assessment factors bring many challenges to the handling of drug products. Rafik Bishara reviews the global perspectives in regulatory oversight on pharmaceutical time and temperature products.



How best to use stability data
for handling of time and
temperature sensitive products
by Claude Ammann
<https://vimeo.com/51441321>
running time: 10:08 min (2011)

Claude Ammann reviews the importance of understanding regulations related to the stability testing to add value to evaluate temperature excursions.

How does a VVM work?

by Denis Maire

<https://vimeo.com/58747176>

running time: 08:39 min (2012)



Denis Maire summarizes the technical characteristics of VVMs and explains how they work.

Interpretation of VVM in relation
to other temperature monitoring
devices

by Umit Kartoglu

<https://vimeo.com/58156915>

running time 12:49 min (2012)



Umit Kartoglu reviews temperature monitoring devices used in a typical vaccine cold chain and analyzes how the readings relate to each other when there are more than one device at a particular point. This analysis is done from the VVM perspective.

Introduction to
Quality Risk Management

by James Vesper

<https://vimeo.com/51441324>

running time: 12:28 min (2011)



Risk management involves a series of activities that are sequenced so that one step informs or shapes those that follow. James Vesper provides a high-level overview of the entire process.



Last Mile
by Umit Kartoglu
<https://vimeo.com/51442652>
running time: 11:15 min (2011)

Umit Kartoglu reviews the critical last mile between the service point and the end user. He further discusses the best solutions for storage and transport of products and best practices for temperature monitoring.



Nothing stands still
by World Health Organization
<https://vimeo.com/51505482>
running time: 17:50 min (2008)

The video of the WHO-PDA Pharmaceutical cold chain management on wheels course conducted during 2-7 June 2008 in Istanbul, Ankara, Konya, Eskisehir and Bursa (1,400 km route) in Turkey.



Packaging design
by Kevin O'Donnell
<https://vimeo.com/56557204>
running time 09:42 (2011)

Kevin O'Donnell discusses the features of nylon, EPS, PUR, airliner and VIP packaging technologies.

Risk assessment methods

by James Vesper

<https://vimeo.com/51441322>

running time: 18:23 min (2012)



James Vesper goes into details of methods frequently used in risk assessments and gives first hand advice on when and how best to them: Preliminary risk assessment, failure mode effects analysis and fault tree analysis.

Shake and Tell (video article)

by World Health Organization

<https://vimeo.com/8381355>

running time: 22:17 min (2010)



This is the first ever video of a full-fledged scientific article on the validity of the shake test. Shake test is the only test available to diagnose whether a freeze-sensitive vaccine has been damaged by freezing.

Step-by-step how to conduct the shake test

by World Health Organization

<https://vimeo.com/54449730>

running time: 10"07 min (2010)



This educational video provides the steps of a standard validated way of performing a shake test and interpreting the results.



Storage Facility Design:
Cold Storage
by Andrew Garnett
<https://vimeo.com/51444653>
running time: 12:03 min (2011)

Andrew Garnett reviews the cold storage aspects of storage facility design and covers temperature controlled storage areas, order assembly areas and materials handling.



Storage Facility Design:
Site and Buildings
by Andrew Garnett
<https://vimeo.com/51442645>
running time: 11:59 min (2011)

Andrew Garnett reviews the storage facility design with a particular emphasis on the site and buildings through analysing the reasons for storing cold chain products, different types and functions of storage facilities, location, access, security, general building design issues.



Thermodynamics
by Kevin O'Donnell
<https://vimeo.com/51444284>
running time: 08:53 min (2011)

Kevin O'Donnell discusses thermodynamics, the basis of heat transfer and how we can use heat energy to our benefit in packaging.

Using VVM as a stock
management tool

by Umit Kartoglu

<https://vimeo.com/58161022>

running time 08:22 min (2012)



Umit Kartoglu reviews the requirements for product arrival, storage and dispatch and analyzes the role of VVM in effective stock management for each step. Special emphasis is given to the relation of VVM and expiry date in illustrating how VVM overrules earliest expiry first out principle.

Vaccines beyond the cold chain

by Simona Zipursky

<https://vimeo.com/58148555>

running time 12:48 min (2012)



Simona Zipursky reviews the studies on taking vaccines beyond the cold chain all published in peer-review journals and comments on how VVMs could be instrumental in these operations.

VVMs getting smarter

by Umit Kartoglu

<https://vimeo.com/58161023>

running time 03:32 min (2012)



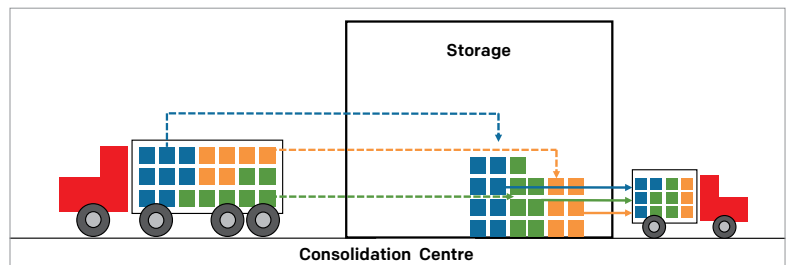
Umit Kartoglu reviews the recent changes in integrity and location of VVMs and the new message VVM is giving whether a vial containing multi-dose vaccine can be kept for a subsequent session following opening the vial.



VVM use at the most periphery
by Serge Ganivet
<https://vimeo.com/58680045>
running time 03:45 min (2013)

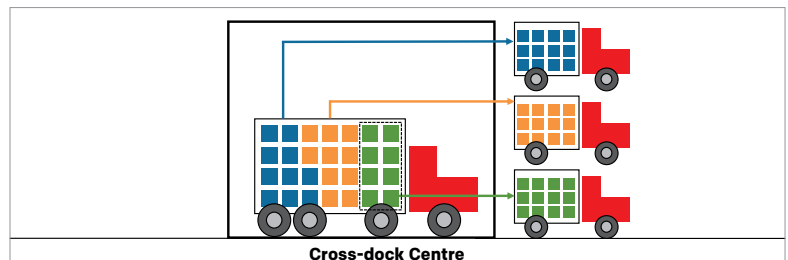
Serge Ganivet reviews the VVM use at the most periphery through different examples and brings new perspectives on how to make best decisions based on the expiry and VVM readings.

GIFs



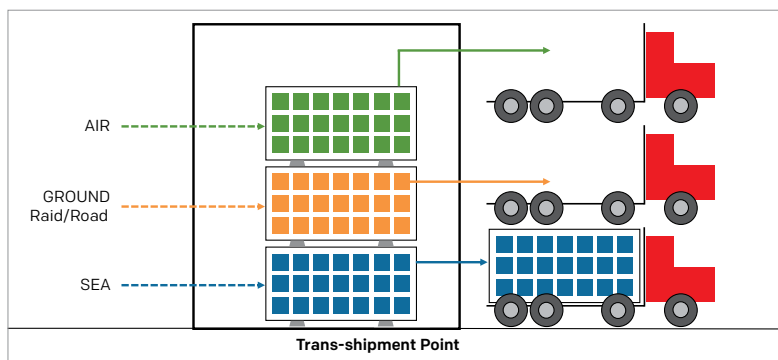
Consolidation centre

<http://epela.net/illustrated/gifs/consolidation.gif>



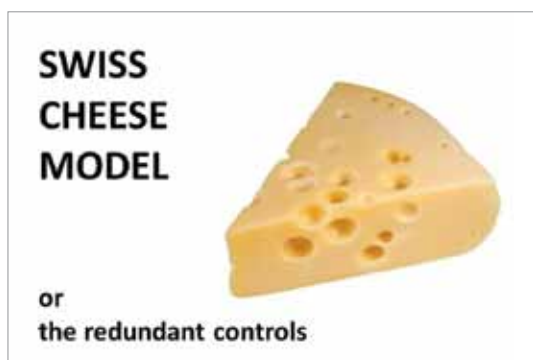
Cross-dock centre

<http://epela.net/illustrated/gifs/crossdock.gif>



Trans-shipment point

<http://epela.net/illustrated/gifs/transshipment.gif>



Swiss cheese model

<http://epela.net/illustrated/gifs/swisscheese.gif>

About the Author



Ümit Kartoğlu is a medical doctor and a scientist at the World Health Organization Headquarters in Geneva.

Ümit began his career in Turkey, where he served at all levels of the national health system for over 10 years. He joined UNICEF in 1994 and has been with WHO since 2001.

Ümit has brought to life the WHO-UNICEF Effective Vaccine Store Management initiative, Global Training Network for Vaccine Management, and the Performance, Quality and Safety (PQS) project. Currently Ümit is coordinating the Global Learning Opportunities (GLO) network.

Ümit has developed a variety of courses, tools and games for learning. He received six international awards in the field of research and communication, including the 2010 IQPC Cool Chain Excellence Award and the 2011 and 2013 Ludwig Rajchman Public Health Award. Ümit was named as one of the "Temperature Controlled Logistics Leaders for 2012" by the IQPC's Temperature Control Logistics & Quality Network, an international industry peer group recognizing 15 of the most influential and inspiring thought leaders in global pharmaceutical supply chain. He also received the 2015 Golden Award in e-learning category of the Hermes Creative Awards for e-Pharmaceutical Cold Chain Management course.

Pharmaceutical and vaccine quality

ILLUSTRATED

"An expert on risk management is said to have a poster on his office wall with two theorems of communication:

Theorem 1. One-half of the world's problems are caused by people using the same word for different things.

Theorem 2. The other half of the world's problems are caused by people using different words for the same thing.

*If you have facilitated group meetings, written guidelines, or led training sessions, you probably have experienced those problems. And, if you have, this book, **Pharmaceutical and Vaccine Quality Illustrated**, will be a valuable addition to your bookshelf. Dr. Kartoğlu has researched a long list of terms important in pharmaceutical and vaccine manufacturing, distribution, and quality and provided clear definitions. He has used his skills as an illustrator and photographer to make certain terms and concepts even easier to understand. Even if you haven't experienced terminology confusion, this book is still extremely valuable as a reference tool and information source. Simply browsing through it will make you smarter."* **James Vesper**

"From "ABC analysis" to the "Zeroth law of thermodynamics," and everything in between, this compendium of 730 technical terms accompanied by numerous compelling illustrations will prove to be an invaluable resource for professionals and practitioners concerned about the quality, purity, safety and suitability of pharmaceutical products. You don't have to be an expert in this field (and I am not one) to recognize the dedication, effort, and caring that Dr. Kartoğlu has put into this masterful work. Making this resource freely available to anyone in the world through a Creative Commons license makes the caring aspect of Dr. Kartoğlu's dedication and effort all the more evident." **Thomas Reeves**

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