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# Stability - Regulatory Requirements

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Stability requirements in  
Drug Substances / Drug  
Products for Submission  
to Regulated /  
Semi Unregulated Markets



# Stability – Retest Period / Shelf Life

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Minimum Period till when the product

- Is safe to use
- Retains its quality
- Retains its efficacy
  
- For chemicals – retest period
- For formulations – shelf life (no reprocessing)



## Criteria for Acceptable Levels of Stability

Type of Stability	Conditions Maintained Throughout the Shelf Life of the Drug Product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties, including appearance, palatability, uniformity, dissolution and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
Therapeutic	The therapeutic effect remains unchanged.
Toxicological	No significant increase in toxicity occurs.

<1191> STABILITY CONSIDERATIONS IN DISPENSING PRACTICE



# Stability Requirements - Proof

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Stability data –

- To prove the quality of the product till expiry
- Evaluation of quality of
  - product under extreme conditions for definite time
  - product under normal conditions for life time
  - product under intermediate conditions for definite time
  - product under particular conditions plausible for definite time



# Stability and Storage

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- Primary packaging
  - Factors affecting integrity of Primary Packaging
  - Factors affecting packaged formulations
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- Storage conditions
  - Environmental factors
  - Storage condition requirements



# Storage & Environment – Regional Aspects

- Different environmental conditions in different part of the globe
- Effect on primary packaging will be different
- Discussions, Consensus, Differences of Opinions
- Global stability requirements – harmonisation ?
- Zones and sub-zones ICH + WHO



<b>CZ</b>	<b>Definition</b>	<b>Criteria</b> Mean annual temperature / Mean annual partial water Vapour Pressure	<b>Long-term Testing conditions</b>
I	Temperate climate	$\leq 15^{\circ}\text{C} / \leq 11 \text{ hPa}$	$21^{\circ}\text{C} / 45\% \text{ RH}$
II	Subtropical and Mediterranean Climate	$> 15 \text{ to } 22^{\circ}\text{C} / > 11 \text{ to } 18 \text{ hPa}$	$25^{\circ}\text{C} / 60\% \text{ RH}$
III	Hot and dry climate	$> 22^{\circ}\text{C} / \leq 15 \text{ hPa}$	$30^{\circ}\text{C} / 35\% \text{ RH}$
IVA	Hot and humid climate	$> 22^{\circ}\text{C} / > 15 \text{ to } 27 \text{ hPa}$	$30^{\circ}\text{C} / 65\% \text{ RH}$
IVB	Hot and very humid climate	$> 22^{\circ}\text{C} / > 27 \text{ hPa}$	$30^{\circ}\text{C} / 75\% \text{ RH}$



# Analysis and Stability Data

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- Sampling points
- Matrixing and Reduced Testing
- Duration of Stability Study
- Extrapolation of Data
- Trend Analysis
- Determination of Shelf Life / Re-test Period
- Stability Commitment



# Stability Guidance

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- WHO
- ICH
  - USA
  - EU
  - Japan
- Brazil
- ASEAN



# ICH

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- Exhaustive guidance
- Joint group of with the help of and three regulatory bodies – USA, EU, Japan
- Guidance for Drug Substance and Drug Product
- Guidance for dosage forms, package style (permiabile / semi-permiabile-non-permiabile, transparent / light resistant)
- Stress testing
- Duration of study
- Sampling points
- Matrixing and bracketing (reduced testing)



# ICH

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- Protocol
- Specification
- Reporting style
- Tabular summary
- Data compilation
- Statistics and derivation
- Shelf life / re-test period
- Stability commitment



# USA

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- Exhibit batch stability data as per ICH guidance
- Accelerated – API – 6 M / Formulation – 3 M
- Intermediate – API – 6 M / Formulation – 3 M
- Long Term – API – 6 M / Formulation – 3 M
- Stability Commitment
- Stability of Validation Batches
- Annual Stability Commitment



# EU

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- Stability data for 3 batches (2+1)
- As per ICH guidance
- Accelerated – Formulation – 6 M
- Intermediate – Formulation – 6 M
- Long Term – Formulation – 6 M
- Stability Commitment
- Stability of Validation Batches
- Packaging Validation / Stability
- Annual Stability Commitment
- Individual country requirements ?



# JAPAN

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- Follows ICH guidance
- Used to require stability data on three batches right before submission for approval
- Language and cultural barrier



# JAPAN

## Matrixing and Bracketing – general case

	Package or Formulation
Formulation or Package 1	Sampling Pattern 1
Formulation or Package 2	Sampling Pattern 2
Formulation or Package 3	Sampling Pattern 1

Sampling Pattern	Batch	Testing Point (month)							
		0	3	6	9	12	18	24	36
1	A	○	○	○	○	○	○	○	○
	B	○	○	○	○	○	○	○	○
	C	○	○	○	○	○	○	○	○
2	A	X	X	X	X	X	X	X	X
	B	X	X	X	X	X	X	X	X
	C	X	X	X	X	X	X	X	X

○: test; X: no test

- International Stability Testing – David J Mazzo



# BRAZIL

Dosage Form	Storage Conditions	Packaging	Temperature and Humidity criteria	
			Accelerated	Long-Term
Solid	15°C - 30°C	Semi-permeable	40°C ±2°C / 75% RH ±5% RH	30°C ±2°C / 75% RH ± 5% RH
	15°C - 30°C	Impermeable	40°C ±2°C	30°C ±2°C
Semi-solid	15°C - 30°C	Semi-permeable	40°C ±2°C / 75% RH ±5% RH	30°C ±2°C / 75% RH ±5% RH
	15°C - 30°C	Impermeable	40°C ±2°C	30°C ±2°C
	15°C - 30°C	Semi-permeable	40°C ±2°C / 75% RH ±5% RH	30°C ±2°C / 75% RH ±5% RH
Fluids	15°C - 30°C	Impermeable	40°C ±2°C	30°C ±2°C
Gases	15°C - 30°C	Impermeable	40°C ±2°C	30°C ±2°C
All Dosage Forms	2°C - 8°C	Impermeable	25°C ±2°C	5°C ±3°C
	2°C - 8°C	Semi-permeable	25°C ± 2°C / 60 % RH ± 5% RH	5°C ±3°C

Many sub-conditions are present (e.g. weigh-loss calculation of semi-solid at 75% RH)



# ASEAN

- Exhaustive as ICH
- All points as in ICH covered
- Storage conditions different
- Data on minimum 2 batches (for standard products)
- 3 batches for NCE, modified dosage forms, unstable APIs
- Formats for Protocol, Report, Summary etc
- Bracketing :

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container size (ml)	15	T	T	T				T	T	T
	100									
	500	T	T	T				T	T	T



# INDIA

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- Schedule M
- Point 16.10 -

The Quality Control Department shall conduct stability studies of the products to ensure and assign their shelf-life at the prescribed conditions of storage. All records of such studies shall be maintained.



## Case Study - Srilanka

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- Co-relation of labeling and stability data
- Data at temperature condition of 25°C unacceptable for label stating “Store below 30°C”
- Long time stability study at 30°C

## Case Study - Sudan

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- Temperature conditions requirement – 50° C



# Stability Specifications

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- Some countries insist on some specific tests to be included in the Stability Specification
- Hardness
- Preservative efficacy
- Microbial Purity



# Labeling

<b>Limiting factors</b>	<b>Additional labeling statement, where relevant</b>
Pharmaceutical products that cannot tolerate refrigerating	“Do not refrigerate or freeze”
Pharmaceutical products that cannot tolerate freezing	“Do not freeze”
Light-sensitive pharmaceutical products	“Protect from light”
Pharmaceutical products that cannot tolerate excessive heat, e.g. suppositories	“Store & transport always below 30°C”
Highly hygroscopic pharmaceutical products	“Store in dry condition”



# Stability and Packaging

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- USA – HDPE Bottles
- EU – Blisters / HDPE Bottles
- India – No bottles
  
- Primary / Secondary Packaging
- Injectable
- Special Packaging
- Silica Gel



# Stability - Various

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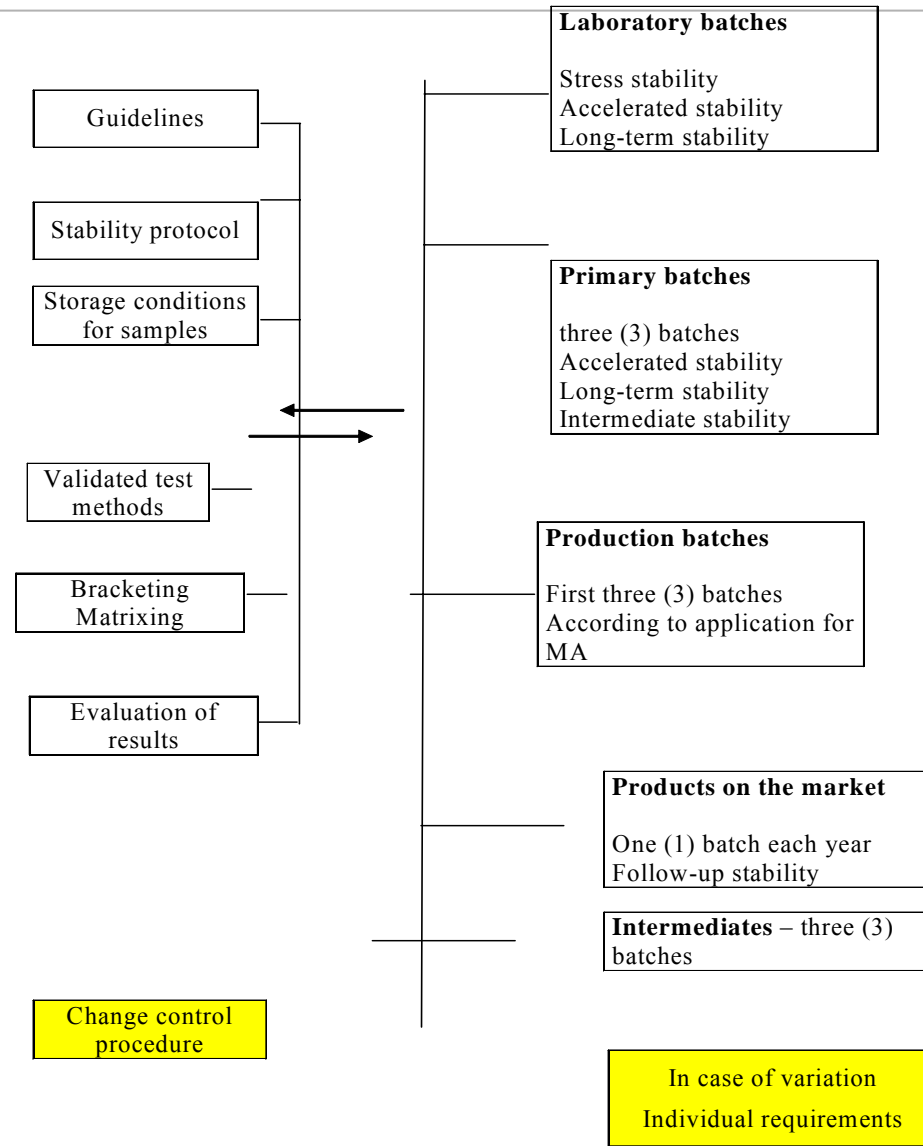
- Shipping Stability
- Hold Time Study



# DRUG PRODUCT STABILITY TESTING SYSTEM

## MAJOR FACTORS

## PLANNING OF STABILITY TESTING



*Thank you !!!*

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