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*The Standard of Quality*SM

Welcome

Quality Standards for Medicines | Dietary Supplements | Food Ingredients

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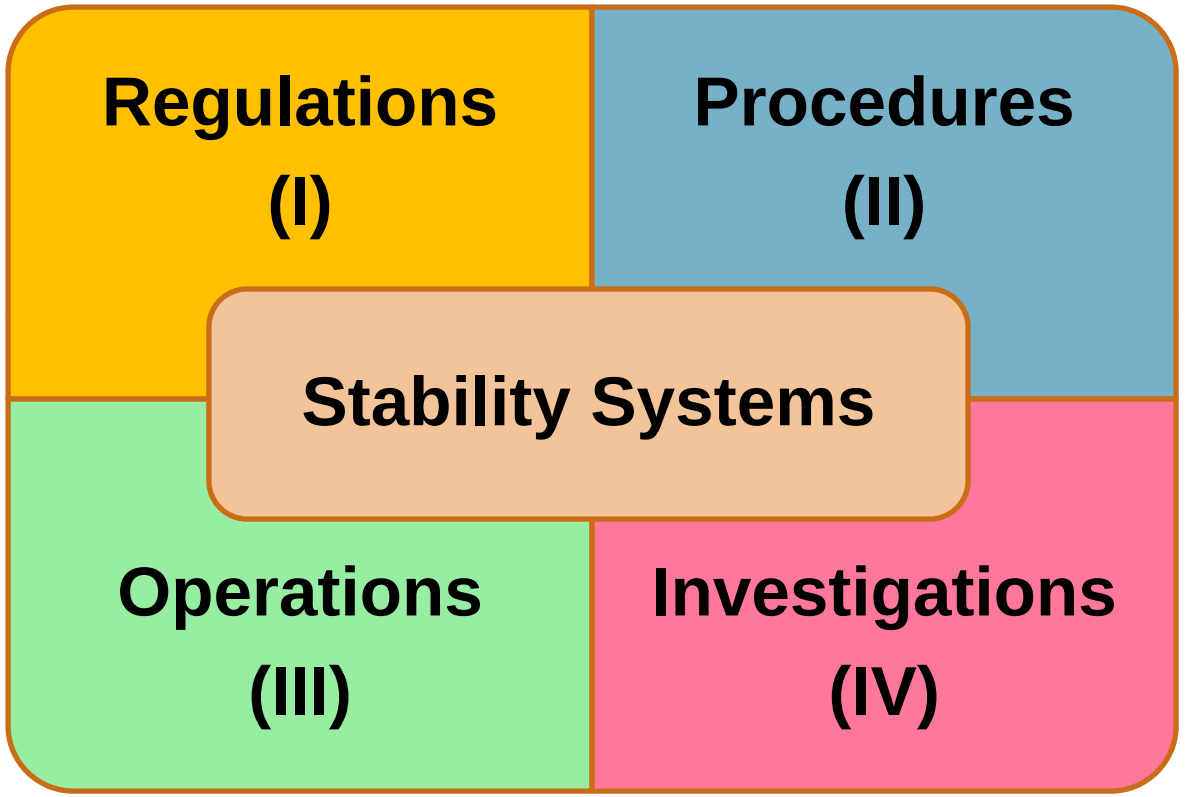
Stability Program for Pharmaceuticals Products

September 2013
Presented for US Pharmacopeia

Critical Stability Systems



Agenda – Day One

- **I. Understanding cGMPs of Stability Testing Requirements**
  - Critical role of Drug Stability
  - Impact of Chinese GMPs on Stability
  - Impact of 21 CRF 211 on Stability
  - ICH process and Q1AR2
  - Stability protocol for global submission

- **II. Developing Stability Indicating Test Methods**
  - ICH Q2 A/B on Validation
  - USP <1225> Validation
  - Method verification based on USP<1226>
  - Stability-indicating test methods

Agenda – Day Two

- **III. Critical Stability Operations**
- Critical steps of Stability Process
- Reduce testing with bracketing and matrixing
- Benefits and drawbacks of bracketing and matrixing
- Stability Data Evaluation

- **IV. Conduct Out-of-Spec investigation for Stability Results**
- FDA draft guidance on OOS and FDA Guides to inspection
- Analyst's and supervisor's roles in OOS investigation
- Out-of-Trend for Stability Data
- Determine Corrective Actions/Preventive Actions

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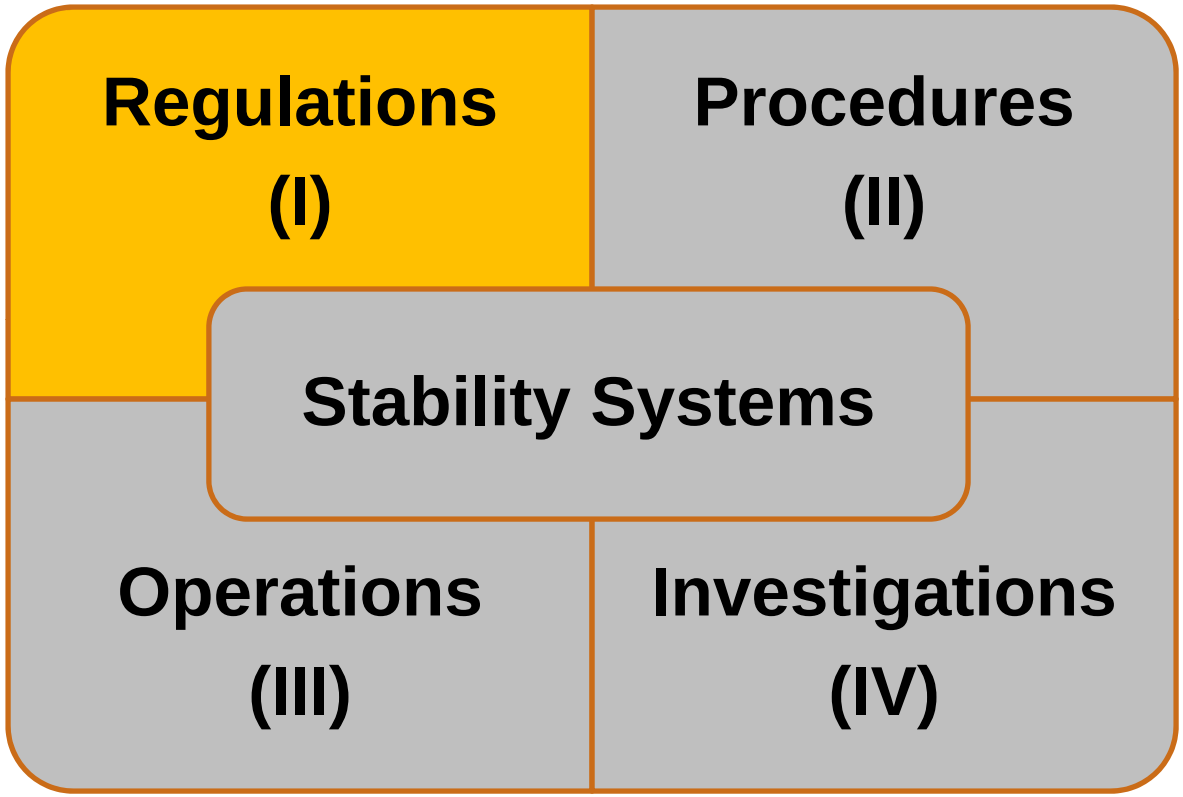
I. Understanding cGMPs of Stability Testing Requirements

Critical Stability Systems



Types of Medications

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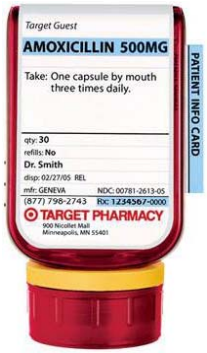
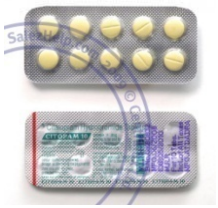
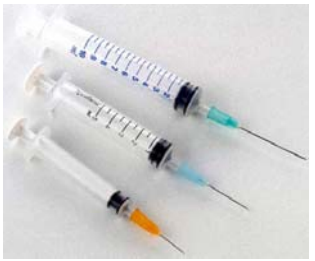
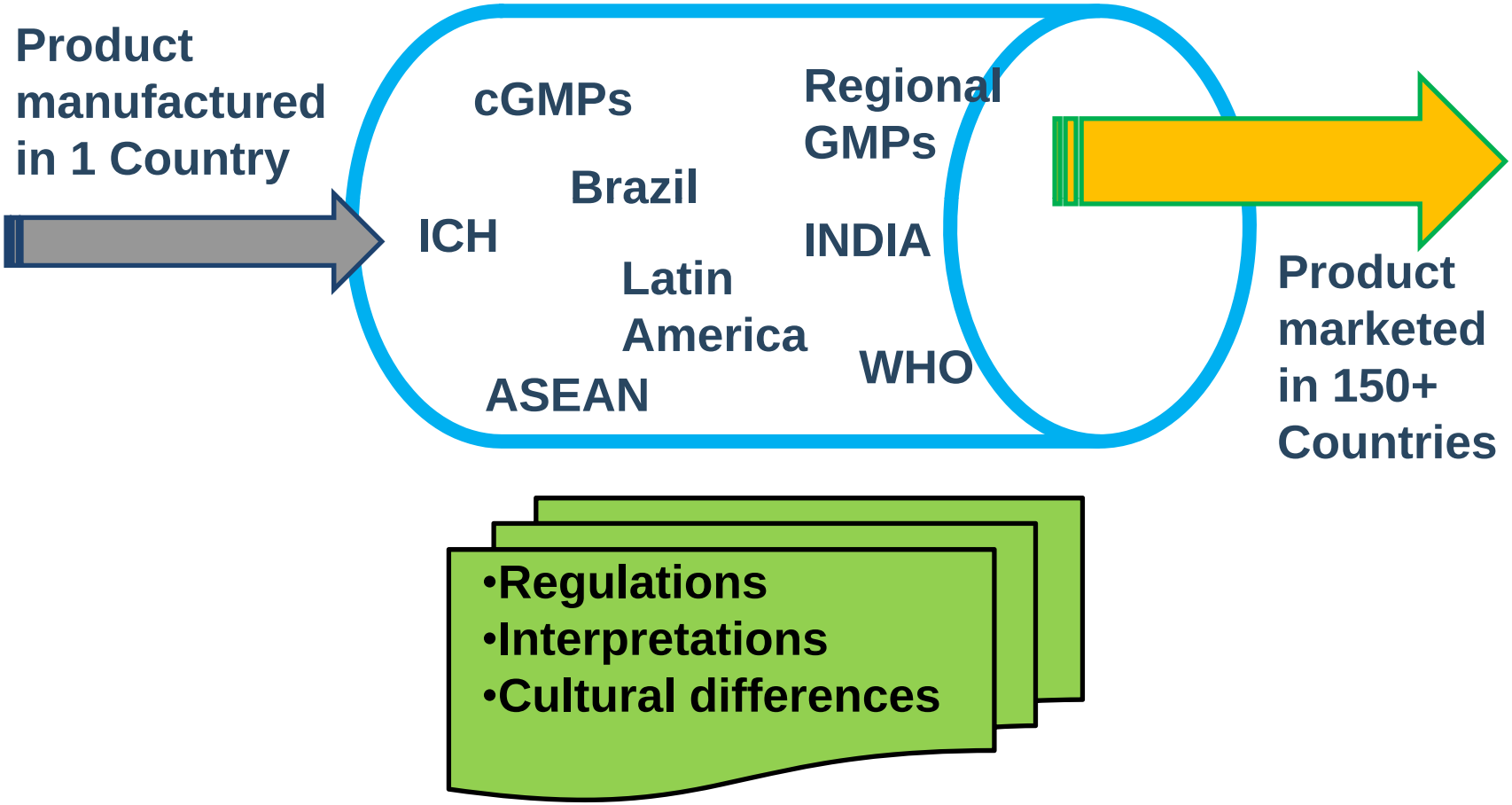


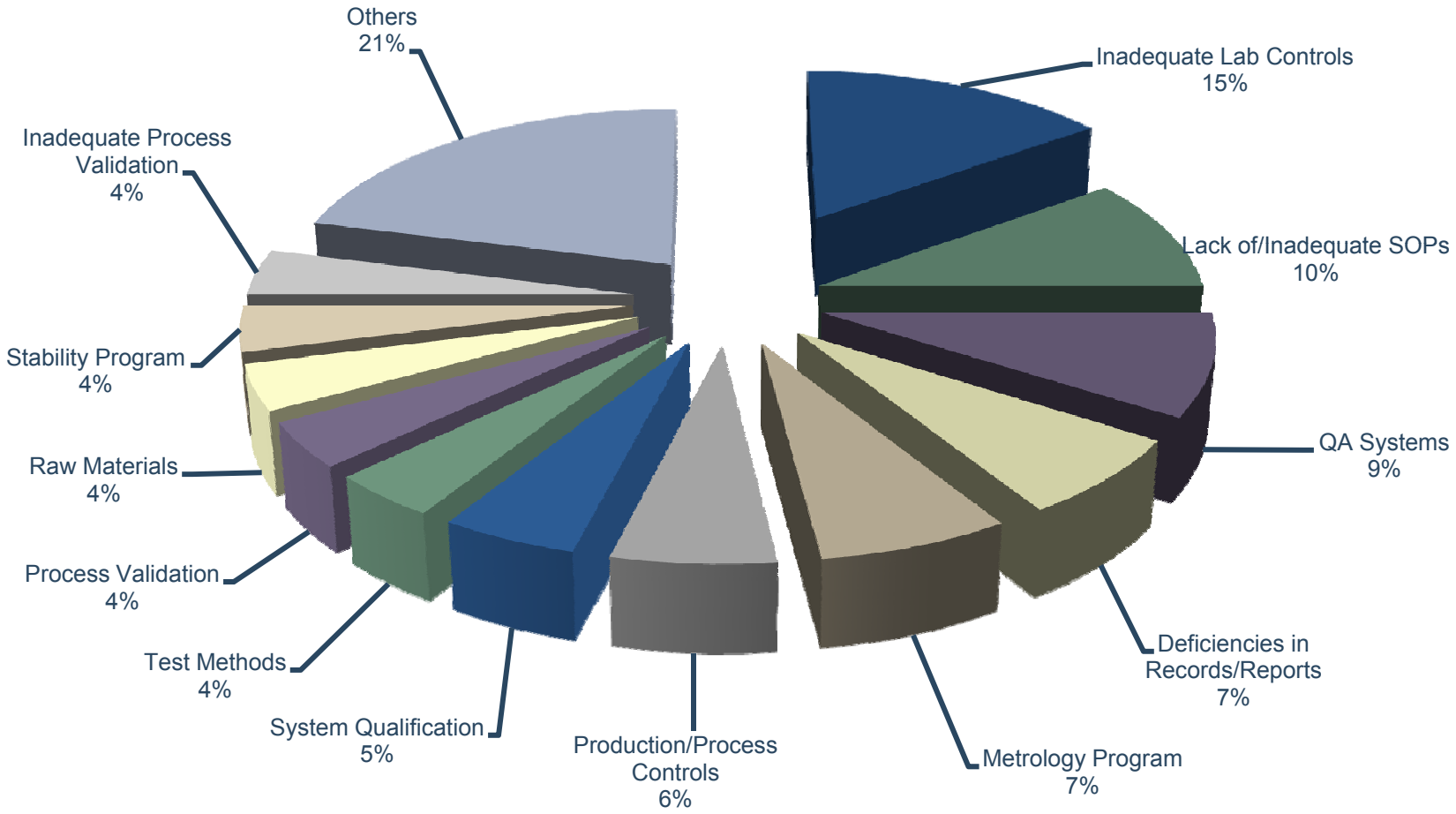




Product Development



Recent inspection data (2012)



Price of Medicines

- On average 5 out of 5000 new drug candidates are tested in human and only one (1) is approved.
- Average cost of bringing one medicine on the market is 800M to 1.2 Billions
- It takes 10-12 years to discover and develop a new medicine
- Cost of research increase significantly
- Cost of law suits and litigations
- Cost of marketing and advertising

Stability Goals

- ACTIVE PHARMACEUTICAL INGREDIENT (API)
  - To establish a retest date for API
  - Data to support submission of drug product

- DRUG PRODUCT
  - To establish a shelf life for the commercial product

Drug Product Stability

- Stability characteristics of API or Drug Product is a critical quality attribute of pharmaceutical product
- Stability Studies are used to support the development of necessary medical supplies

Critical Role of Drug Stability

- Safety and efficacy of drug product are established during development via clinical studies
- Quality is established for identify, strength, quality and purity (CFR 211.137)
- If drug product stability changes beyond established acceptance criteria, established safety and efficacy are no longer applicable.

Drug Product Stability

- Stability Data are used to:
  - Establish how product changes over time under critical environmental factors (temperature, humidity and light)
  - Determine appropriate product specifications
  - Select marketing container closure system
  - Determine appropriate storage conditions
  - Justification of expiry of commercial product

Change of Drug Stability

- Change of Drug Stability would risk patient safety
  - Quality of finished products decrease
  - Potential sub-potent or over-dose products
  - Potential toxic unknown impurities
- Uncontrolled process → product investigation → product recalls
- cGMP violations → consent decree → criminal prosecution

Factors affecting Drug Stability

API related:

- Stability of the API from storage
- Interaction between the API and excipient – FD
- Effect of storage (temperature, humidity and light)

Factors affecting Drug Stability

Process related:

- Selection of different dosage form
- Manufacturing process of drug product (DP)
- Selection of marketing image

Factors affecting Drug Stability

Packaging related:

- Selection of container closure packaging system
- Handling of DP
- Distribution of DP
- Marketing regions

DRUG DEVELOPMENT PROCESS

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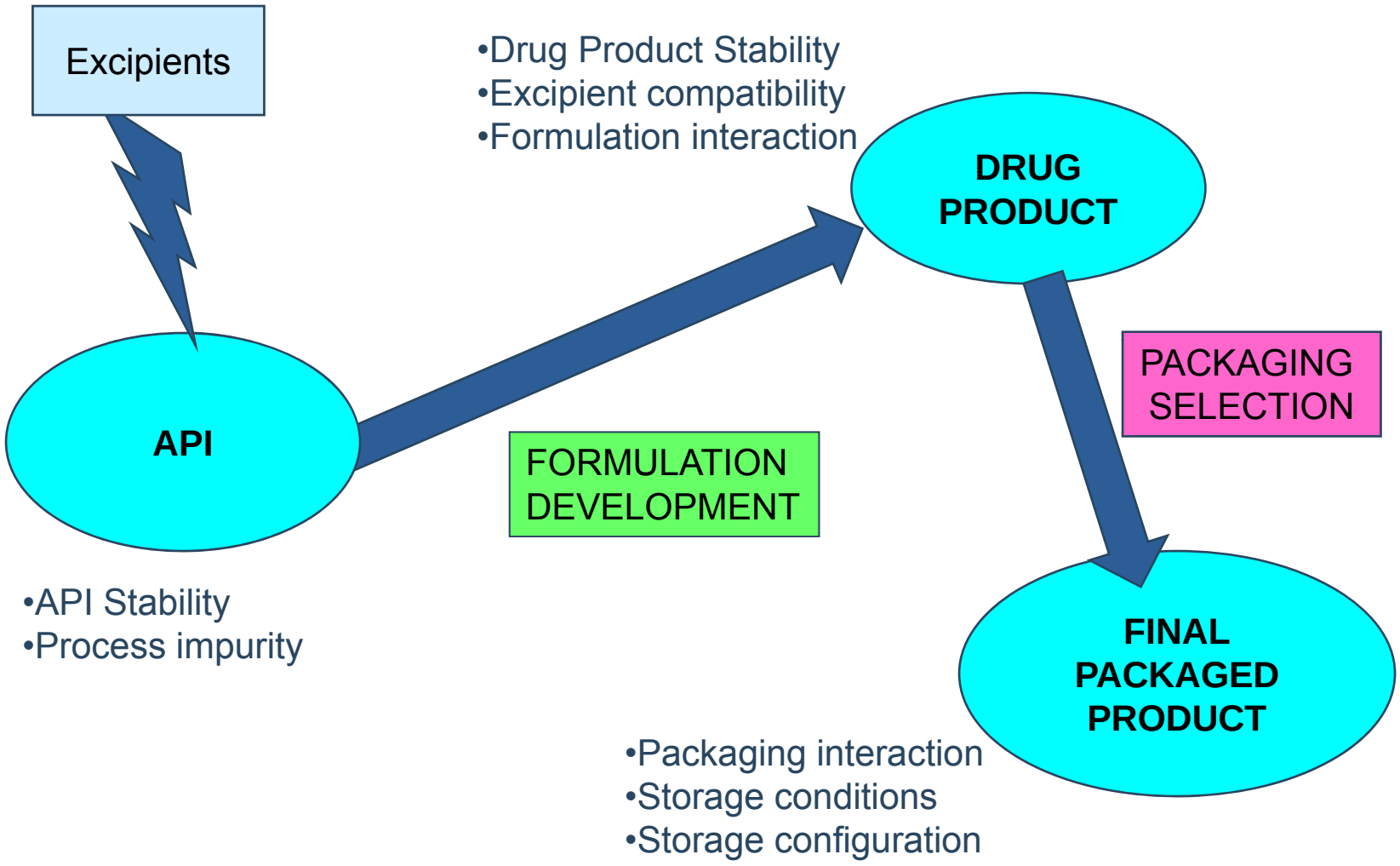

Purpose of Stability Testing

- The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.

- Stability testing permits the establishment of recommended storage conditions, retest periods, and shelf-lives.

ICH harmonized Tripartite Guideline for Stability Testing of New Drug Substances and Products [ICH Q1AR2]

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GMP - 21 CFR 211

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PART 211--cGMP Practices for Finished Pharmaceuticals

- Sec. 211.1 SCOPE (a) The regulations in this part contain the minimum current GMP practice for preparation of drug products for administration to humans or animals.

PART 211--cGMP Practices for Finished Pharmaceuticals

- Sec. 211.137 EXPIRATION DATING

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in Sec. 211.166.

21 CFR 211.166 - Stability Testing

- Stability program must be written and followed:
  - (a) used in determining appropriate storage conditions and expiration date.
  - Written program must include: Sample size and test intervals, Storage conditions for samples,

21 CFR 211.166 - Stability Testing

- Stability program must be written and followed (cont'd):
  - Reliable, meaningful, and specific test methods,
  - Testing of drug product in marketed container,
  - Testing of drug product for reconstitution at dispensing time and reconstituted time.

211.166 Stability Testing

- (b) An adequate number of batches must be tested to determine an appropriate expiration date. A record of such data must be maintained.

211.166 Stability Testing

- Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates.
- Full shelf-life studies, if not available, are being conducted.

USP General Information Chapters

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Three critical components of Documentary Standards

1. Monographs
2. General Chapters
3. General Notices

USP General Information Chapters

- Consist of chapter <1000> and upwards
- Chapters provide information – they contain no standards, tests, assays, nor other mandatory specifications, with respect to any Pharmacopeial articles

<1150> Pharmaceutical Stability - Obsolete

- Apply to drug dosage form
- Chemical, physical & micro integrity of the unit
- Shelf life = initial preparation to expiration
- Specifications (identity, strength, quality and purity) throughout shelf life
- Influenced by environmental conditions (temperature, light, air, and humidity)

- **REMOVED from USP34.**

Controlled Room Temperature

- Labeled “controlled room temperature” or “upto 25°”
- Maintain MKT not more than 25°
- International guideline 25 +/- 2° at 60 +/- 5% RH
- Accelerated 40 +/- 2° at 75 +/- 5% RH
- MKT

- <1150> Pharmaceutical Stability was removed
- Added to General Notices

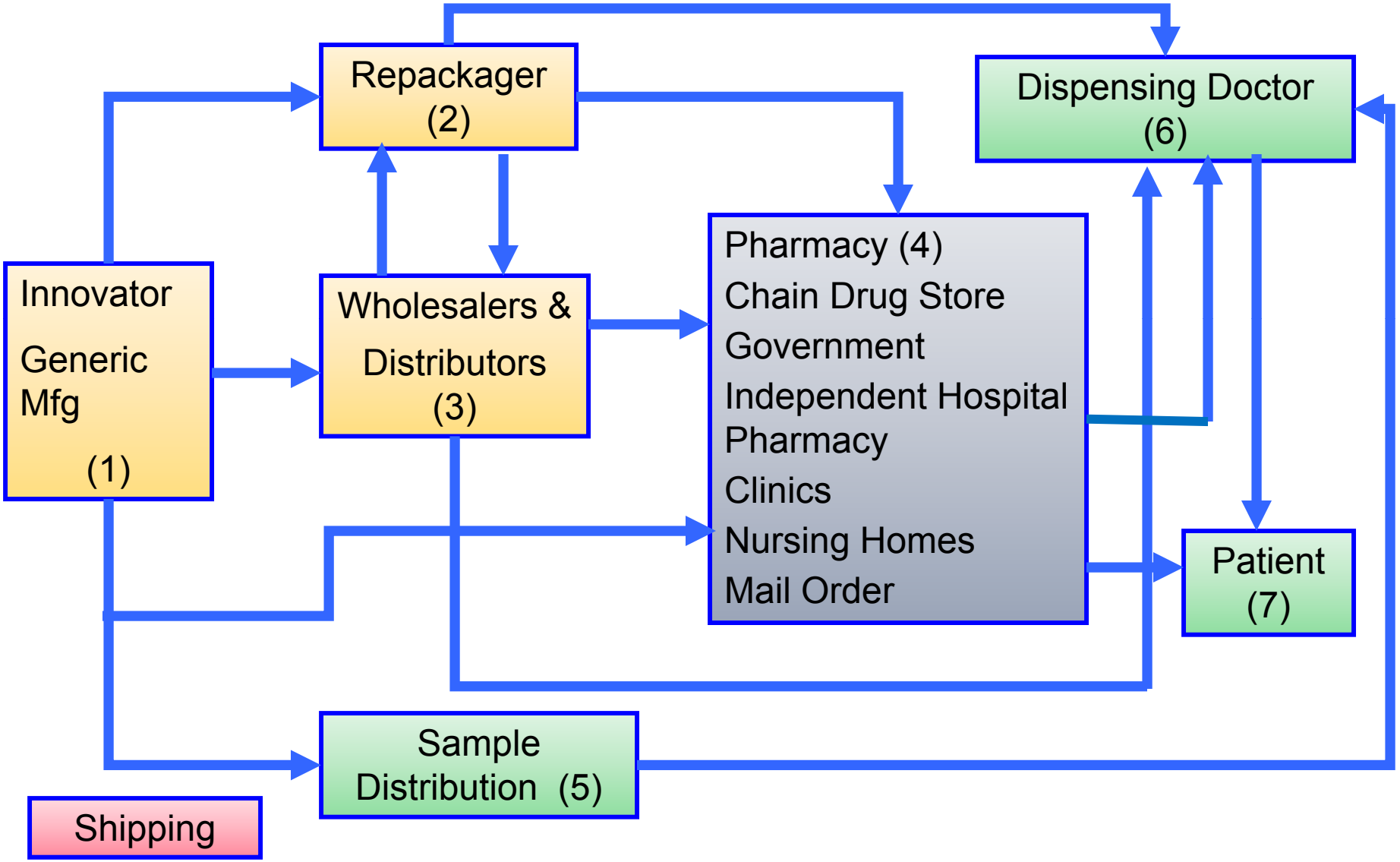
Mean Kinetic Temperature

$$T_k = \frac{\Delta H/R}{-\ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)}$$

ΔH = the heat of activation for the degradation reaction; assumed to be 83.144 kJ per mol unless more accurate information is available from experimental studies.
$R = 8.3144 \times 10^{-3}$ kJ per degree per mol (the universal gas constant)
T_1 = the average temperature, in degrees Kelvin, during the first time period
T_2 = the average temperature, in degrees Kelvin, during the second time period
T_n = the average temperature, in degrees Kelvin during the nth time period

- <1150> Pharmaceutical Stability was removed
- Added to <1079> Good Storage and Shipping Practices

Drug Product Distribution



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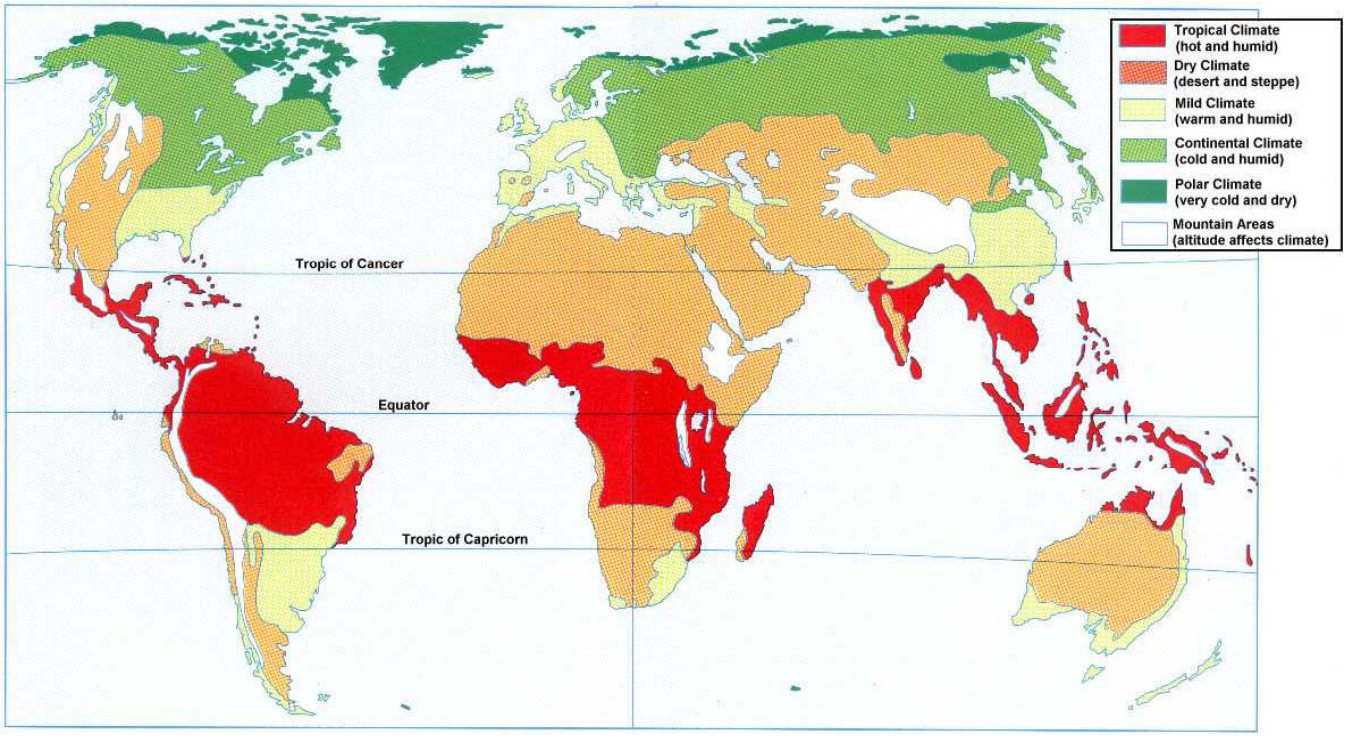
ICH Stability -- Q1A (R2)

International Conference on Harmonization (ICH)

- Purpose: To provide a forum for dialogue between Health Authorities and Industry on the disparities with respect to requirements of US, Europe and Japan



Global Stability Requirements

Global Climatic Zones

- Zone I: Temperate less than 20°C
  - e.g. Germany, Russia, Canada
- Zone II: Sub-tropical with possible high humidity
  - averaging 20.5-24°C
  - e.g. France, Peru, Australia, USA
- Zone III: hot and dry
  - e.g. Botswana, Chad, Syria, Iraq
- Zone IV: hot and humid
  - averaging more than 24°C
  - e.g. Taiwan, Singapore, India, parts of South America

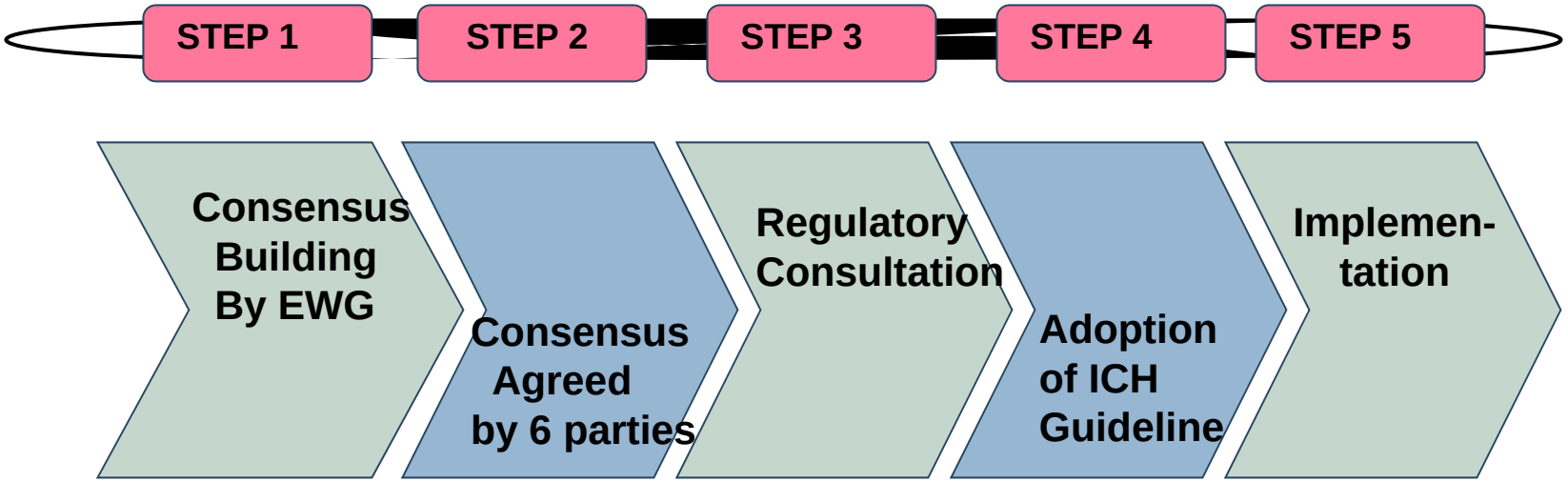
International Conference on Harmonization (ICH)

- Goal: To develop guidelines that are acceptable for regulatory review by US, Europe and Japan
- ICH Steering Committee: 6 Parties
  - PhRMa, FDA,
  - EFPIA, EU,
  - MHLW, JPMA
  - and IFPMA (non voting member)
  - Official Observers: Canada, WHO, EFTA
  - Interested Parties: Pharmacopeia, IGPA, WSMI

ICH participants

- FDA – US Food & Drug Administration
- PhRMA – Pharmaceutical Research and Manufacturers of America
- EU – European Union
- EPPIA – European Federation of Pharmaceutical Industries and Associations
- MHLW – Ministry of Health, Labour and Welfare
- JPMA – Japan Pharmaceutical Manufacturers Association
- IFPMA – International Federation of Pharmaceutical Manufacturers & Associations
- WHO – World Health Organization
- EFTA - The European Free Trade Association
- WSMI – World Self-Medication Industry
- IGPA – International Generic Pharmaceutical Alliance

5 Major Steps in ICH Process



- Harmonizing Stability Storage Conditions
- Registration requirements

Handbook of Stability Testing in Pharmaceutical Development: Regulations, Methodologies and Best Practices, K. Huynh-Ba (ed.), Springer, November 2008, Chapter 2.

Distribution of nations into different climatic zones

Region	Zones I & II	Zone III & IV
European	All countries	-
American	Chile, Canada, United States	Brazil, Jamaica, Venezuela
Asian	China, Japan, Turkey	India, Philippines, Sri Lanka
African	South Africa, Zambia, Zimbabwe	Botswana, Ghana, Uganda
Australian / Oceanic	Australia, New Zealand	Fiji, Papua - New Guinea

ICH Storage Conditions

Intended Storage Condition	Stability Studies	Study Condition	Submission Requirement
Room Temperature	Long Term	25 °C/60 %RH	12 months
	Intermediate*	30 °C/65 %RH	6 months
	Accelerated	40 °C/75 %RH	6 months
Refrigerated	Long Term	5 °C/ ambient	12 months
	Accelerated	25 °C/60 %RH	6 months
Freezer	Long Term	- 20 °C/ ambient	12 months

* Significant change

Selection of Batches

	API	DRUG PRODUCT
Selection of Batches	3 batches (pilot scale)	3 batches/strength (2 pilot + 1 lab scale)
Manufacturing Process	Representative of Commercial Production	
Acceptance Criteria	Similar to those used in pre-clinical and clinical studies	
Container Closure	Same to proposed commercial packaging	
Testing Frequency	Long Term: 0, 3, 6, 9, 12, 18, 24 mo and annually Intermediate: to 12 months, minimum 4 points Accelerated: to 6 months, at least 3 points	
Stability Commitment	Must commit to put up 3 production batches with same protocols	

Significant Change

API	Significant change is defined as failure to meet the specification.
Drug Product	1. A 5 percent potency change from the initial assay value;
	2. Any specified degradant exceeding its acceptance criteria
	3. Failure to meet acceptance criteria for appearance and physical properties (e.g., color, phase separation, resuspendibility, delivery per actuation, caking, hardness); and as appropriate to the product type;
	4. The pH exceeding its acceptance criteria; and
	5. Dissolution exceeding the acceptance criteria for 12 dosage units.

Other Stability Storage Condition

Other stress conditions

- 30°C/90%RH (3-6 months)
- 50°C (3-6 months)
- 60°C (3-6 months)
- Photostability (Q1B)
- Freeze-Thaw
- Thermal Cycling

Global Stability Requirements

- Example of temperature excursion studies:
  - Thermal Cycling
    - e.g., 40°C, 4 days, then 25°C/60%RH, 3 days
    - Repeat cycle twice
  - Freeze-Thaw Cycling
    - e.g., -20°C, 4 days then 25°C/60%RH, 3 days
    - Repeat cycle twice
- Perform full testing at end of complete cycling

Handbook of Stability Testing in Pharmaceutical Development: Regulations, Methodologies and Best Practices, K. Huynh-Ba (ed.), Springer, November 2008, Chapter 2.

Special Package

- Liquids in Semi-Permeable Containers:
  - Long-Term: 25°C/40±5%RH (Zone I/II) *or*
    30°C/35±5%RH (all zones)
  - Intermediate: 30°C/65±5%RH
  - Accelerated: 40°C/NMT25%RH

*or 25°C/60RH and calculate wt. loss equiv. to 25°C/40RH

**if 30°C/35RH is long-term condition, no intermediate condition is needed

Global Stability Requirements

- Alternative approach when thermal cycling and free-thaw cycling have not been done
  - Evaluate MKT
  - Review Forced Degradation data
  - Evaluate Stress studies

Key Factors of Q1A(R2)

- Must use Validated Stability-Indicating analytical methods
- Methods must cover *physical, chemical, biological and microbiological* attributes
- Studies evaluated under thermal and elevated humidity to cover storage, shipment and subsequent use

Key Factors of Q1A(R2) (cont'd)

- Accelerated and intermediate used to evaluate impact of short-term excursions.
- Acceptance criteria should include individual and total upper limits for impurities and degradation products
- No formal statistical analysis is needed if data show little degradation or variability.

Photostability (Q1B)

Expose sample to a range of radiation that simulates sunlight.

Specification: Visible radiation is not less than 1.2 million lxh and UV is not less than 200 W h/m^2

- Option I:
  - single radiation source
  - more difficult to control temperature/humidity
  - sample will overexposed to UV
- Option II :
  - two radiation sources, one for visible radiation and one for UV
  - easier to control temperature/humidity

Q1B Photostability

- Sequence of studies:
  - Drug products fully exposed, if unacceptable change, proceed to next step
  - Drug products in the intermediate pack, if unacceptable change, proceed to next step
  - Drug products in the marketing pack
- Recommendation on labeling or packaging

ICH Guidances

- Q1C Stability Testing of New Dosage Forms (May 1997);
- Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (January 2003);
- Q1E Evaluation of Stability Data (June 2004);
- ~~Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV, Revision 1 (July 2004) - withdrawn~~
- Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (December 2000);
- Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological (August 1999);
- Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (August 2001);
- Q8 Pharmaceutical Development (Draft) (February 2005);
- M4: Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use (CTD) (October 2001);

- Ref: US FDA, Guidance for Industry on Chemistry, Manufacturing, and Controls Information; Withdrawal and Revision of Seven Guidances, Federal Register 71 (105), 31194-31195 (June 1, 2006) DOCID: fr01jn06-73

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GMP - India

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Personnel

- Head of QC lab is independent of the manufacturing unit
- Personnel of QC and QC are qualified and experienced
- Written duties must be done and following strictly
- Number of people must be adequate and proportional to workload
- Everyone has appropriate training and regular in-service training

Equipment

- Located, designed, constructed, adapted and maintained to suite operations
- Design must minimize risk of errors and allow effective cleaning and maintenance.
- All must have logbook
- Balances to be calibrated and checked
- Part of production equipment that come in contact with product can’t be reactive, additive or adsorptive that effect product quality
- Defective equipment must be removed and appropriate labeled.

Documentation

- Define specs for all materials, manufacturing process, and control process
- Provide audit trail that permit investigation
- Documents designed, prepared, reviewed and controlled
- Documents must be approved, signed and dated by appropriate and authorized personnel.
- Document specify title, nature and purpose.
- Record complete at time of operation
- Data recorded by electronic: data entry, change or deletion, etc..

Validation

- Conducted as per a pre-defined protocol
- Include validation of processing, testing and cleaning procedures
- Written report summarizing results and conclusions
- Significant changes to equipment, materials, methods shall be validated.

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WHO Stability Guidelines

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WHO Stability guidelines

Working document QAS/06.179/Rev.2 – Stability Testing of Active Pharmaceutical Ingredients and Pharmaceutical Products" divides countries with tropical and subtropical moist climates into:

- Zone IVA with long-term conditions: 30°C ± 2°C and 65% ± 5% RH
- Zone IVB with long-term conditions: 30°C ± 2°C and 75% ± 5% RH, which is the worst case and the recommended long-term condition for the Prequalification Project

Each individual Member State within the former Zone IV would need to indicate whether its territory should be classified as Zone IVa or Ivb

- Q1F Withdrawn – 2006
- FDA Withdrawn - Draft Stability Guidelines in 2006

Association of Southeast Asian Nations (A.S.E.A.N.)

**Cambodia,
Brunei,
Indonesia,
Laos,
Malaysia,
Philippines,
Singapore,
Thailand,
Vietnam.**

Climate Zone Classification

Country	Climatic Zones	Assigned To
Afghanistan	I, II	II
Algeria	II, III	II (a)
Angola	II, IV	II
Argentina	II	II
Armenia	I, II	II (a)
Australia	I, II, III, IV	II
Azerbaijan	I, II	II
Bahrain	IV	IV
Bangladesh	IV	IV
Barbados	IV	IV
Belize	IV	IV
Benin	IV	IV
Bolivia	I, II, IV	II (a)
Botswana	III	III
Brazil	II, IV	IV
Bulgaria	I, II	II
Burkina Faso	IV	IV
Burundi	IV	IV
Cameroon	IV	IV
Canada	I	I
Canary Islands	II	II
Central African Republic	IV	IV
Chad	III, IV	III
Chile	I, II	II
China	I, II, IV	II (a)
Columbia	IV	IV
Congo	II, IV	IV

Re-test Period

After this period a batch of API destined for use in the manufacture of a pharmaceutical product should be re-tested for compliance with the specification and then used immediately. A batch of active pharmaceutical ingredient 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.

A retest period should be proposed on the basis of stability results and may be extended to five years

Shelf-Life (Expiration Dating Period)

The period of time during which a pharmaceutical 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.

Stability Protocol

- Study described in a written protocol
- Protocol extented to the end of retest period
- Similar Protocol used for long-term studies and primary batches
- Data must be documented in a report
- API Batches should be manufactured from different batches of intermediates
- DP batches should be made from different API batches

Typical Global Stability Protocol

TEMP HUMIDITY	TZ	1 Mo	2 Mo	3 Mo	6 mo	9 Mo	12 Mo	18 Mo	24 mo	36 Mo
25 C 60%RH	X			X	X	X	X	X	X	X
30 C 65%RH				X	X	X	X	(X)	(X)	(X)
(30 C 75%RH)	X			X	X	X	X	X	X	X
40 C 75%RH		X	(X)	X	X					
50 C				X						
5 C		H	O	L	D					

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Stress Testing

Drug substance (API)

Studies undertaken to elucidate the intrinsic stability of the active pharmaceutical ingredient. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Drug Product (DP)

Studies undertaken to assess the effect of severe conditions on the pharmaceutical product. Such studies include photostability testing and specific testing on certain products, (e.g. metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Goal of stress testing

- To validate the stability indicating power of the analytical procedures.
- To identify stability-affecting factors such as ambient temperature, humidity and light and to select packing materials, which protect the FPP against such effects.
- To identify potential degradants of the API and assess if they can be formed during manufacture or storage of the DP.
- To select manufacturing process of the DP

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Questions