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International Regulatory Harmonisation – A Challenge

Harmonisation in Drug Regulation

- Process of integrating national standards with international standards to be universally acceptable to participating countries to facilitate efficient global drug development and local registration
- Technical and science requirements
- Format and content of dossiers
- Assessment and Review processes

AAPS – Current International Harmonization - JustinaMolzon

Regulatory Environment

Safe. Effective, good quality drugs available
Appropriate information
Rational prescribing
Appropriate dispensing practice

Better treatment of illness
Better prevention of disease
Decreased morbidity & mortality

Drug Regulatory Structures & Processes → Drug Regulation Outcomes → Health outcomes

•Substandard, counterfeit,toxic & Useless drugs
•Inappropriate information
•Irrational prescribing
•Inappropriate dispensing practice

•Drug resistance
•Treatment failure
•Adverse drug reaction
•Increased morbidity & mortality

Drug Regulation & Harmonisation

- Every Regulatory agency has same aim
- Safety, Efficacy and Quality of Drug Product
- Legislations and regulations differ
- Globalisation in true sense – calls for harmonisation

International Regulatory Agencies

- ANVISA
- EMEA / EC
- INVIMA
- JPMA / Kiko
- MCC
- MHRA
- TGA
- US FDA
- Ministries of Health & Welfare etc

Harmonisation Initiatives

- WHO – United Nations
- ICH – USA, EU and Japan
- EC / EMEA – Members of European Union
- PIC/S – 33 Participating Authorities
- ASEAN – 10 Southeast Asian Countries
- PANDRH – Pan American Countries

Subgroups in Harmonisation !

WHO

- The oldest organisation aiming at harmonisation
- Completed 60 years
- Harmonisation of ways to ensure public health
- Currently 193 member countries

ICH

- Europe, USA and Japan – Drug Regulatory Agencies
- First initiative for harmonisation by Regulated Markets for Pharmaceuticals
- Harmonisation in various technical aspects
- CTD – major achievement
- STF – ongoing efforts for review harmonisation

ICH Guidelines

- Efficacy – 13 topics/17 guidelines
- Safety – 8 topics/16 guidelines
- Quality – 9 topics/23 guidelines
- Medical Dictionary – MedDRA
- Electronic Standards – ESTRI, E2B

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Common Technical Docket (CTD)

Regional Harmonisation Initiatives

- **APEC**
  Asia - Pacific Economic Cooperation
- **ASEAN**
  Association of the Southeast Asian Nations
- **GCC**
  Gulf Cooperation Council
- **PANDRH**
  Pan American Network for Drug Regulatory Harmonization
- **SADC**
  Community Southern African Development

Harmonisation

- Various regulatory agencies with different regulations
- All regulations aim for Safety, Efficacy and Quality
- Knowledge sharing among different regulatory authorities
- Method of ensuring and determination differ
- Difference within the Harmonisation initiatives
  e.g. Regulations for BE within members of ICH
- Regional factors (climatic conditions / racial, ethnic and demographic details of population change with region)

Harmonisation

- Interests of Consumer, Industry & Regulators
- Product design for global marketing
- Harmonisation of standards
- Reduce duplication of work
- Reduce resource costs
  - Time
  - Money
  - Material
  - Personnel Resources
  - Testing / Bio-studies
  - Documentations
  - Work inputs

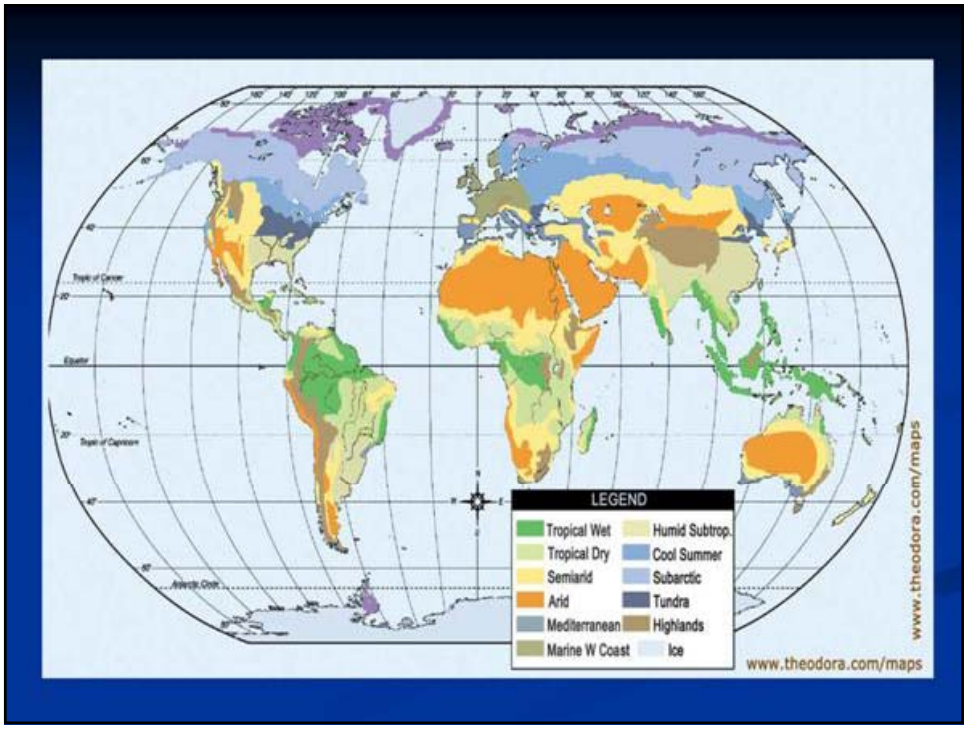
Harmonisation – Indian Industry Perspective

- Strong Pharmaceutical Industry
- Huge potential for trade and exports
- Harmonised regulations for marketing approval beneficial
- Cost benefits
- Effective time management

Harmonisation – Difficulties

- Mutual Recognition Procedures
- Tendency to accept most stringent regulations
- Queries from different member states may require different data which may require different exercises (like tests, studies, study conditions, comparisons etc)
- Compendial requirements differ
- Compendial harmonisation – voluminous task

Harmonisation – Example



Goal of Harmonized Stability - Testing Conditions

- Efforts regionally and inter-regionally to harmonize stability testing conditions
- Biggest Challenge = hot and humid
- Generated much debate as to proper temperature and humidity to predict drug temperature and humidity to predict drug product quality

Stability & Harmonisation

- WHO recommended stability test conditions based on climatic zones

CZ	Climate	Criteria Mean annual temperature in opened air/Mean annual partial water vapor pressure	Long-term Testing Condition
I	Temperate	=15°C /=11hPa	21°C/45% RH
II	Subtropical and Mediterranean	>15-22°C />11-18hPa	25°C/60% RH
III	Hot & Dry	>22°C/=15hPa	30°C/35% RH
IV	Hot & Humid	>22°C/>15hPa	30°C/70% RH

ICH
Stability Data – Climatic Zones III and IV

- ICH Q1F defined storage conditions for stability testing in countries not located in the ICH regions and not covered by ICH Q1A(R2)
- The goal was to harmonize global stability testing requirements by reducing the number of different storage conditions
- 30°C/65% RH was defined as the long –term storage condition for Climatic Zone III/IV (WHO & ASEAN – 70% RH)
- Q1F was adopted by ICH in February 2002 and implemented in ICH regions

Revised Conditions

CZ	Climate	Criteria Mean annual temperature in opened air/Mean annual partial water vapor pressure	Long-term Testing Condition
I	Temperate	=15°C /=11hPa	21°C/45% RH
II	Subtropical and Mediterranean	>15-22°C />11-18hPa	25°C/60% RH
III	Hot & Dry	>22°C/=15hPa	30°C/35% RH
IVa	Hot & Humid	>22°C/>15-27hPa	30°C/65% RH
IVb	Hot & Very Humid	>22°C/>27hPa	30°C/75% RH

Development of Stability Conditions

Year	Guideline	CZ	Long-Term Storage Condition	Intermediate Storage Condition
1993	ICH Q1A	I & II	25°C/60%RH	30°C/60%RH
1996	WHO	III & IV	30°C/70%RH	---
2001	WHO Rev1	III & IV	30°C/65%RH	
2003	ICH Q1A R2	I & II	25°C/60%RH	30°C/65%RH
2003	ICH Q1F	III & IV	30°C/65%RH	
2004/05	ASEAN	IV	30°C/75%RH	
2005	WHO Rev2	III & IVa, IVb	30°C/65%RH	30°C/75%RH
2006	ICH Q1F withdrawn			

Dream

- ✓ Comprehensive and up-to-date drug laws
- ✓ Harmonised but independent organisations
- ✓ Freedom from political and commercial influence
- ✓ Clear and transparent standards and procedures
- ✓ Adequate financial and competent human resources
- ✓ Outcome oriented implementation and systematic evaluation