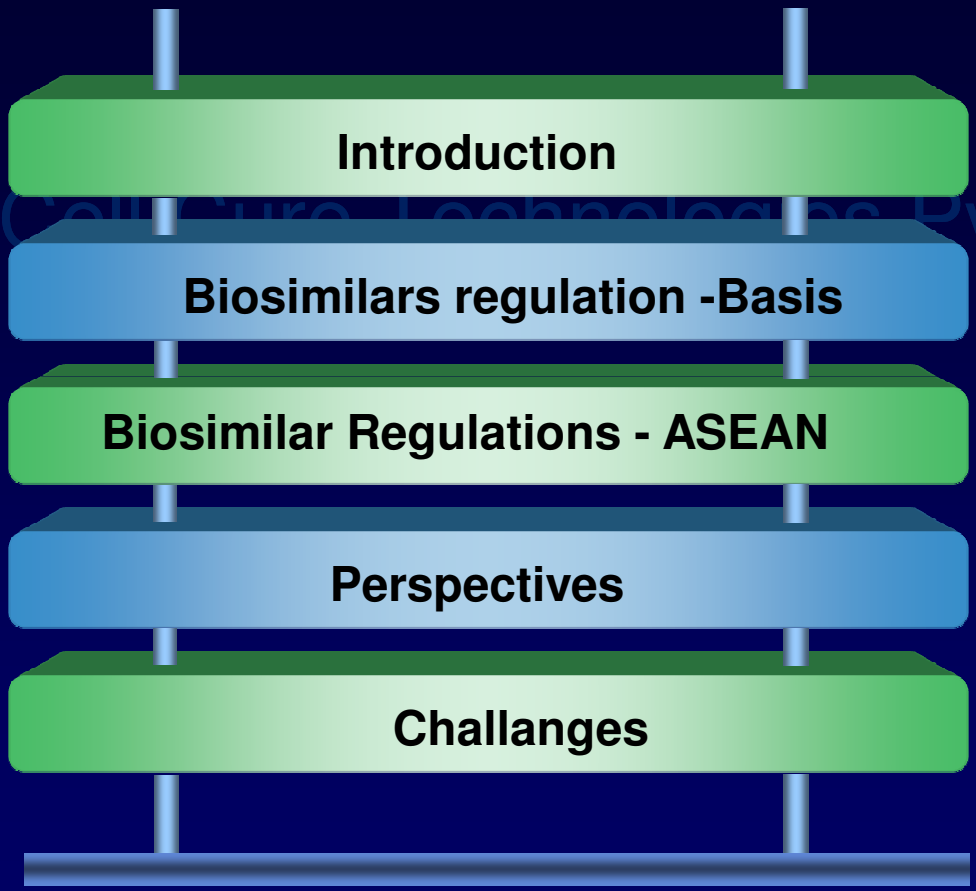
Biosimilar Regulation in the ASEAN

Shivraj Dasari, Ph.D.,
Managing Director,
SLS Cell Cure Technologies Private Limited,
Flat#103, Prabhat Apartments, Street No.11,East Marredpally,
Secunderabad – 500026,Tel/Fax : +91-40-27734415,
www.slscellcure.in Email: drshivraj@slscellcure.in

Contents

SLS Cell Cure Technologies
Predictive Diagnostics & Cell Therapies



SLS Cell Cure Technologies Pvt. Ltd

SLS Cell Cure Technologies
Predictive Diagnostics & Cell Therapies

About Us

Business Streams

SLS Cell Cure Technologies
Predictive Diagnostics & Cell Therapies

Unique Offerings

SLS Cell Cure Technologies Pvt. Ltd

Phase – I
Molecular Diagnostics

- Infectious Disease screening
- Predictive Diagnostics
- Pharmaco-genomics.



Phase – II
Cell Therapies

- Autologous Fibroblast therapy.
- BM derived MSC's
- Cord Blood Derived MSC's
- Peripheral Blood Derived MSC's
- Allogenic Therapies

Molecular Diagnostics is Transforming Medicine

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Molecular diagnostics is >$5 billion market WW and growing at >24% annually

Recurrence monitoring

Drug selection

Disease detection

Disease predisposition

Pre-natal testing

Key questions

"Is the baby healthy? "	"Which diseases is this patient at risk for?"	"Does this patient have disease?"	"What drugs should I prescribe?"	"How the disease relapsed?"

Need for Molecular tests

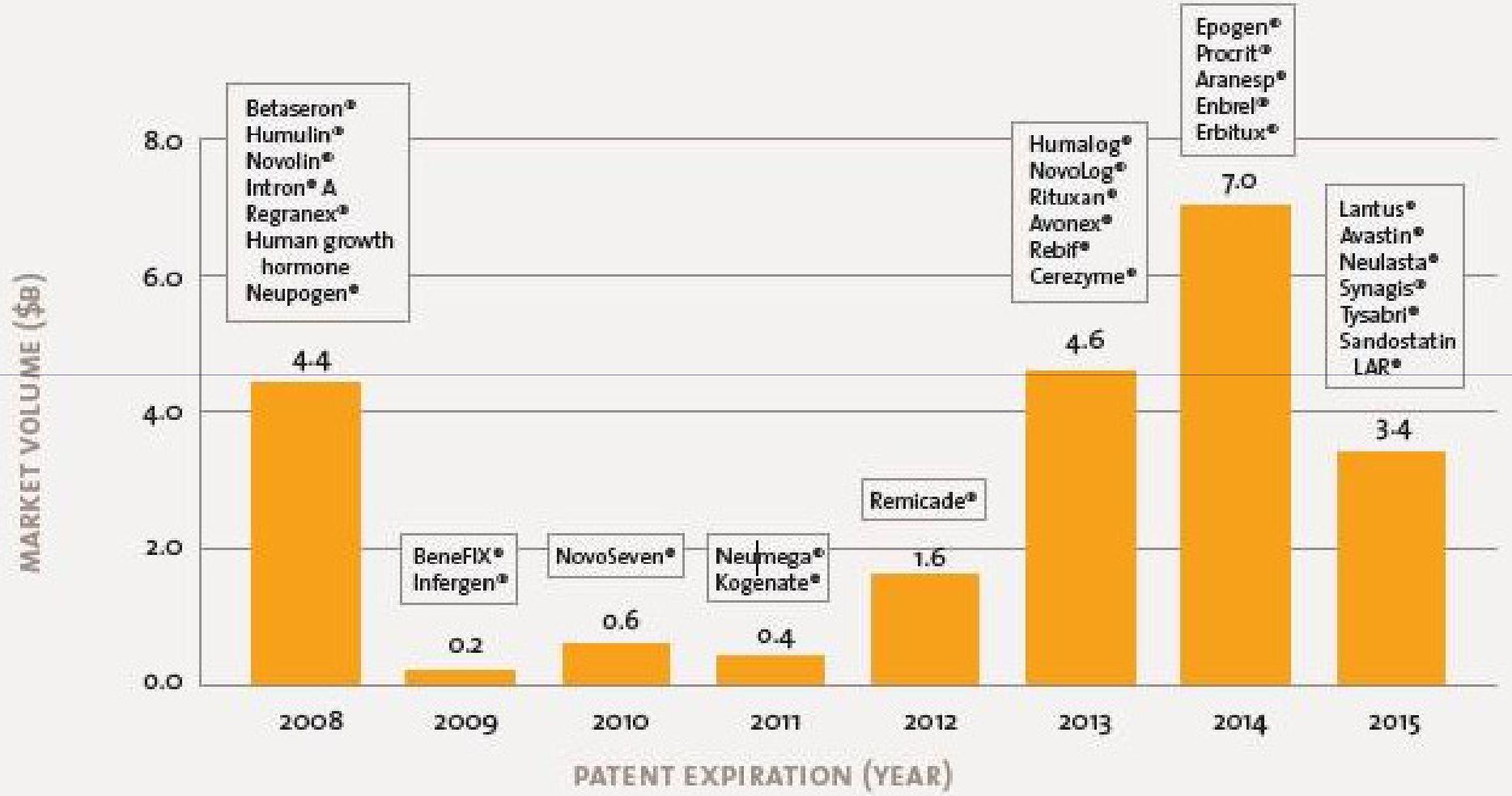
Dr.Shivraj Dasari

SLS Cell Cure Technologies
Predictive Diagnostics & Cell Therapies

Introduction

The expiring patents of blockbuster biologics - creating huge opportunities for biosimilars

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Predictive Diagnostics & Cell Therapies



Of the $60 billion in global revenues from biologics that will lose patent protection by 2015, $17 billion are major blockbusters.

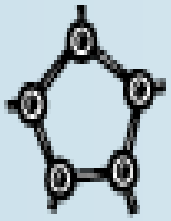
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Predictive Diagnostics & Cell Therapies

Biosimilars – Basis of Regulation

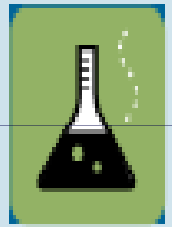
Dr.Shivraj Dasari

Four Things to consider about Biologics

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Molecular Properties



Manufacturing Process



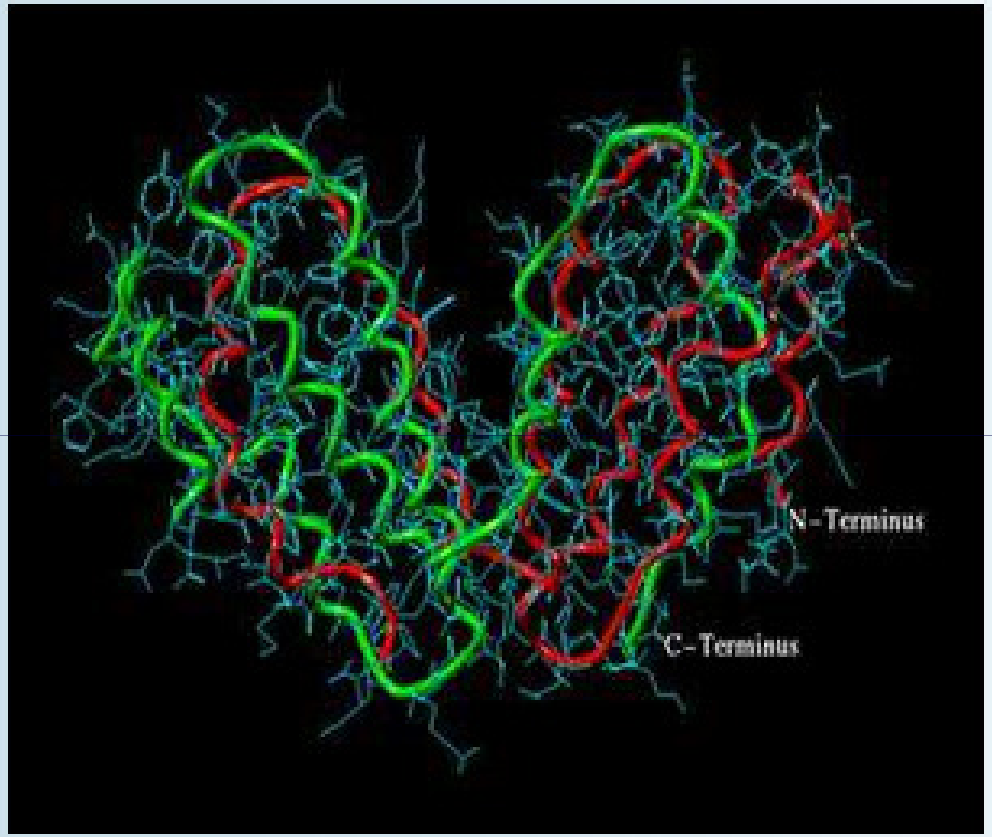
Safety

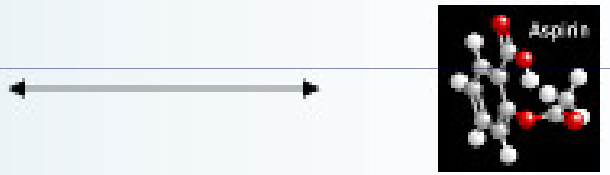


Efficacy

Example: Interferon beta vs Aspirin

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Interferon Beta
MW 19'000D

Aspirin:
MW 180D

Source: Fraunhofer IGB (Interferon Beta)

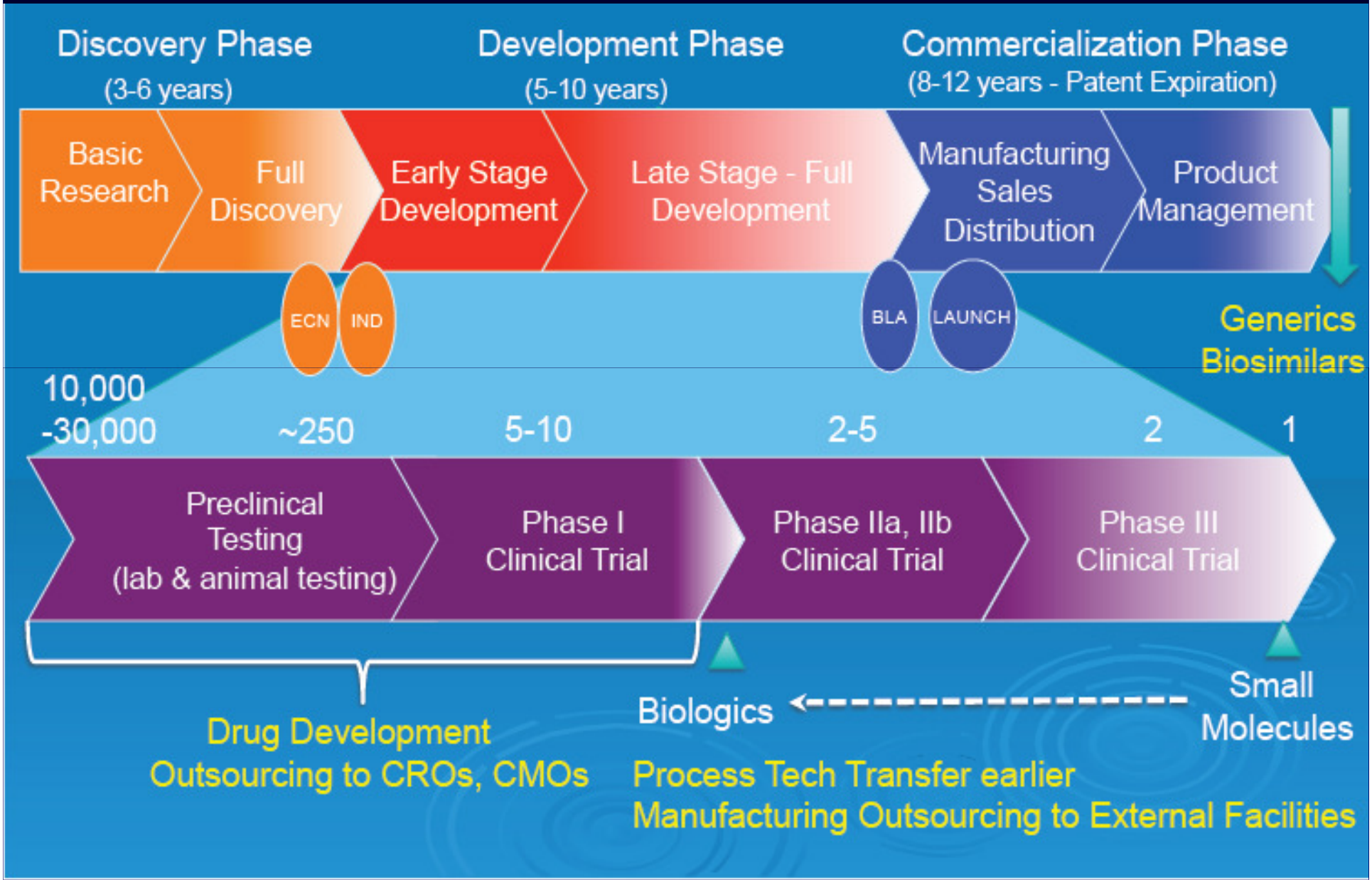
Molecular Properties

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- Biotech Products are more complex than small molecules
- Large molecules, typically 100 to 1000 times larger than a conventional small molecule drug.
- Posses a fragile 3-dimensional structure.
- Not ‘pure’ homogeneous molecules.

Drug Development Process
Paradigm shift for Biologics

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Biosimilars, Bio-generics, follow-on Biologics, Development & Commercialization

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Full Drug Development Capabilities and Infrastructure Required

- CMC: Process development & biologics Manufacturing
- Preclinical and Clinical: Toxicity, Phases 1 and III, comparability studies
- Filing and regulatory challenges

High Barriers to Entry

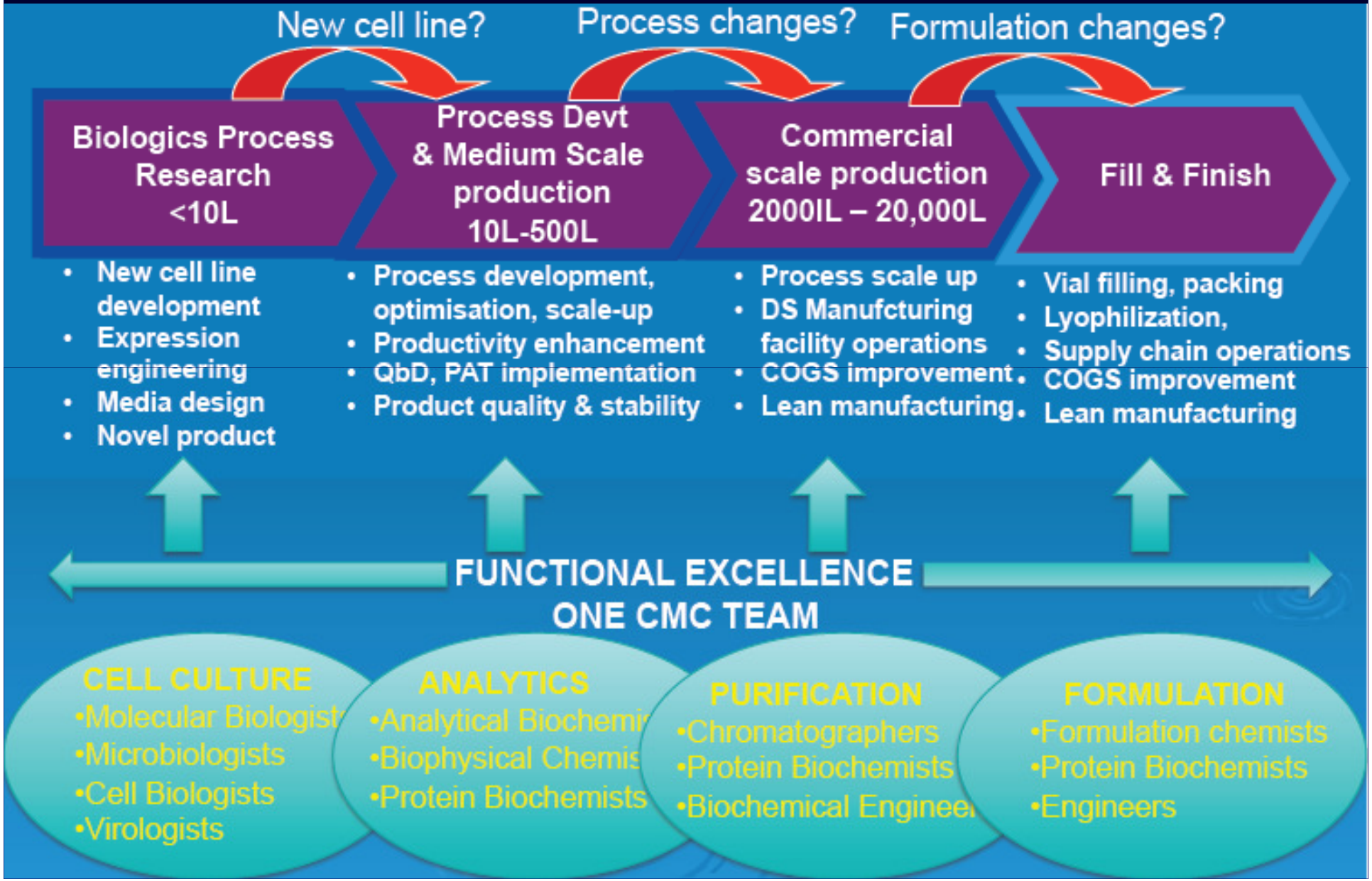
- $50M – $500M long term investment required
- Competition with existing brands (low price differentials)
- Complexity of products (not API) and manufacturing facilities

Highly Competitive Markets

- Large pharmaceutical companies moved in: Merck, Novartis, Aztrazeneca
- Major generics companies formed alliance: Teva & Lonza

Integrate Process Development with Manufacturing

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How are Biopharmaceuticals manufactured?

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- Develop host cell: DNA sequence for protein, select vector to carry the gene, insert this into genome of host(microbial or mammalian cell)
- Establish a cell bank (cell screening and yields)
- Protein production (in spinner flasks and bioreactors)
- Purification (remove endotoxins, viruses, other proteins)
- Analysis (3D structure, aggregation, isoform profile: the way glycosylation is performed, heterogeneity, potency); cannot be fully characterized(not able to detect all characteristics that may affect clinical efficacy and safety)
- Formulation (eg.add stabilizer, HSA or polysorbate)
- Storage and handling (eg. Do not shake, cold chain)

Each of these stages can have a major influence on the characteristics of the end product

Persue Revolutionary technologies to reduce COGS

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High Cell Productivity

TREND:

Higher cell productivity and process optimization result in smaller and less complex manufacturing facilities (20,000L vs. 2,000L)

Process Simplification

- Current mAb platform improvement: Higher capacity resins, One column process, No Protein A
- Chromatography Alternatives
  Crystallization, Ppt, Q filters
- Chemical Process like - Continuous Processing
- Automated sampling and monitoring with new sensors
- Equipment with Integrated instrumentation for real time control and release

Facility Efficiencies

- Using disposable systems reduces SIP and CIP requirements
- Reduction of Process Equipment Size
- Process and facility modularization reduces construction time
- Moving of process equipment into gray space reduces cleanroom space.

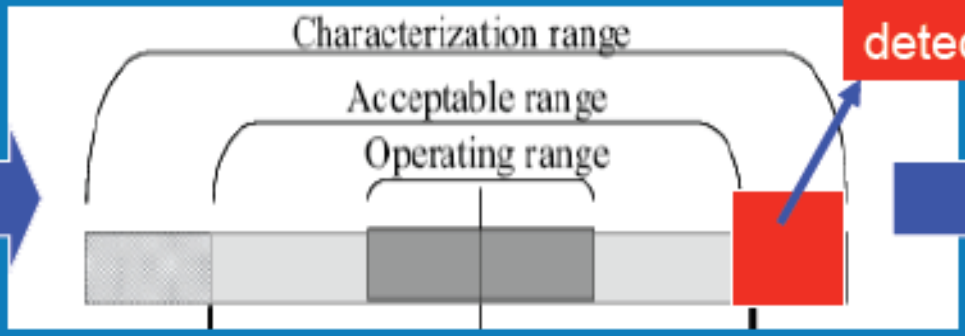
"The Progress of Biotechnology manufacturing and Process Sciences"
Patrick Yang, Genentech, Inc., Nov. 5, 2007, APBioCheDSC, Taiwan.

Early use of QbD & PAT – Knowledge based Process Strategy

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Traditional Approach (fixed controls)

Variability in raw materials, conditions

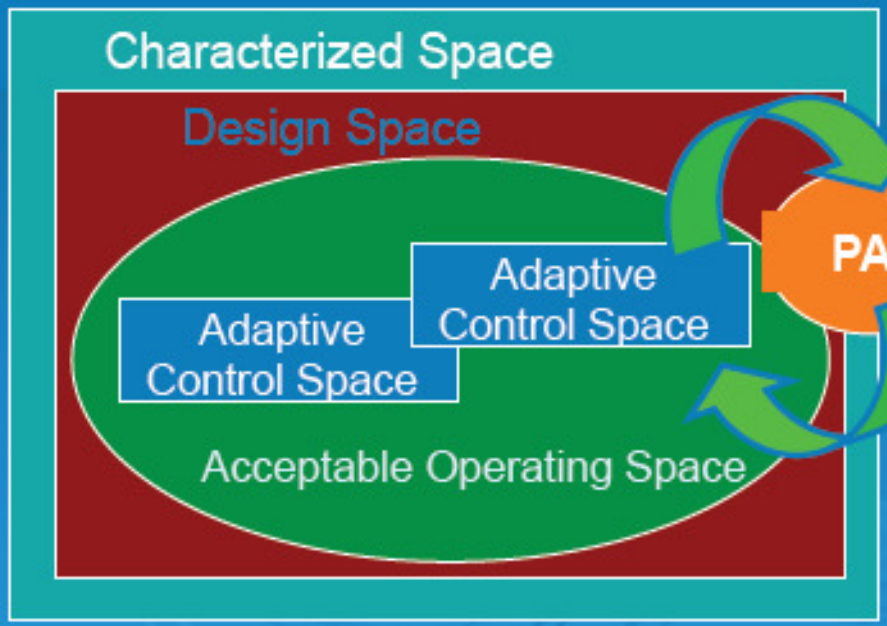


Failures; variation detected late

High variability in product; Possible recalls; Product safety concerns

Dynamic Control Strategy (multidimensional)

Variability in raw materials, conditions



Rapid correction of process parameters

Product consistency; Lower failures

Major Process Challenges

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- **Sterile vs. Aseptic**
  - Requires the application of microbiological contamination control to prevent infectious organisms to be present in the sterile product
- Demonstrate “CONTROL” of the process, while technical complexity increases
  - Characterization to identify variability components
  - Application of science and new technologies
- **Maintenance of the cell lines**
  - Contamination risks
- **Personnel as “incubators”**
  - Source of microbial load



Biologics/Biological Products

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Poorly characterized

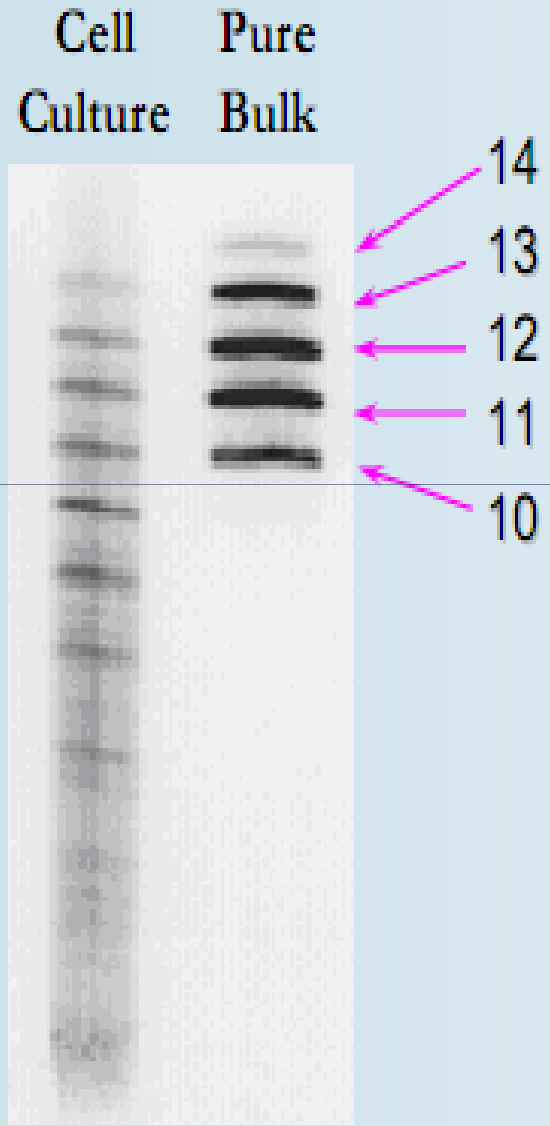
- Traditional vaccines
- Whole blood
- Blood derivatives
- Blood components
- Allergenic extracts
- Stem cells
- Somatic cell and gene therapeutics
- Toxins

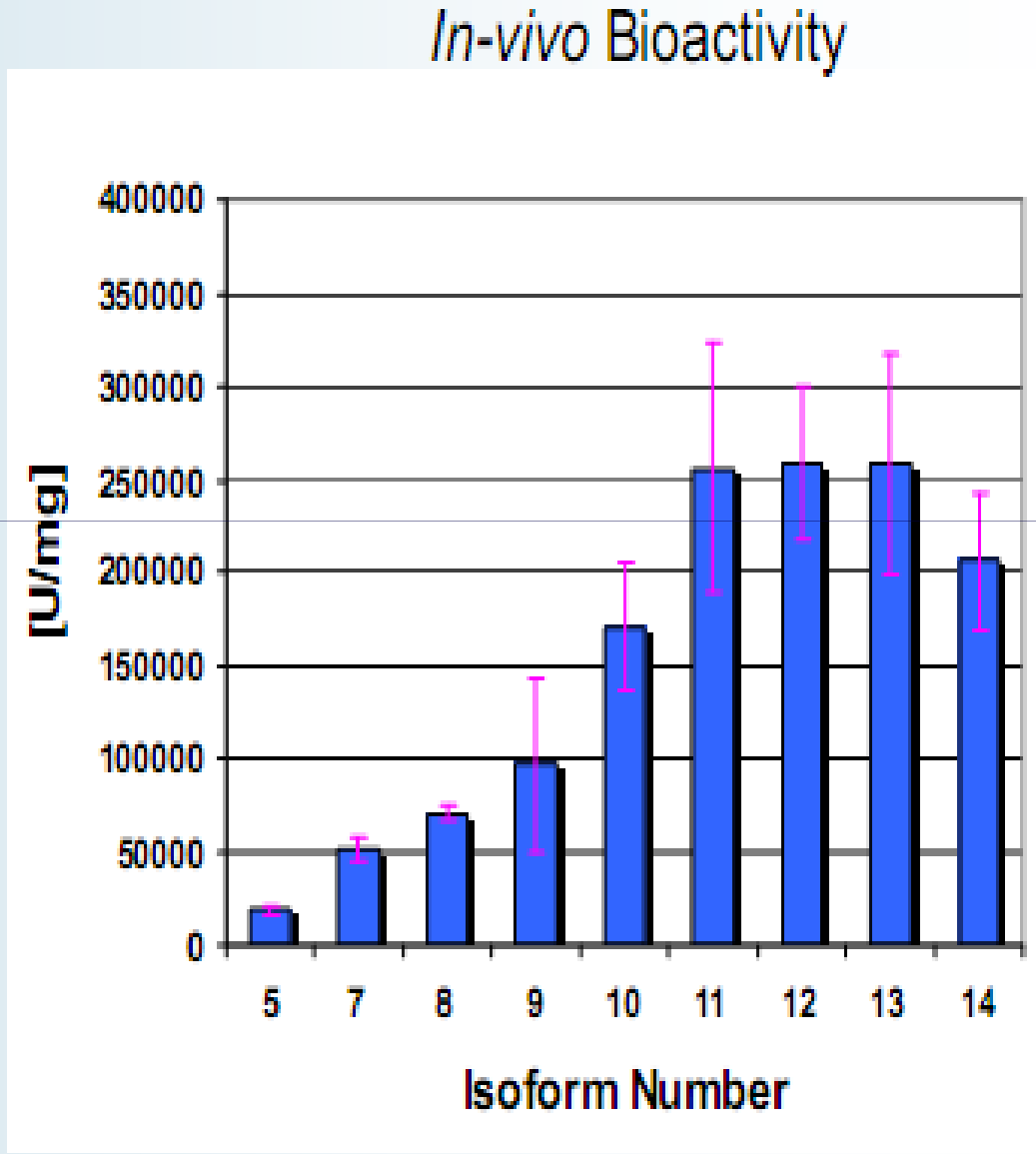
Well-characterized

- Natural proteins
- rDNA-derived proteins
- Monoclonal antibodies
- rDNA-derived vaccines

Biotech medicines do not contain a single active ingredient, they are a heterogeneous mix of different isoforms

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Predictive Diagnostics & Cell Therapies

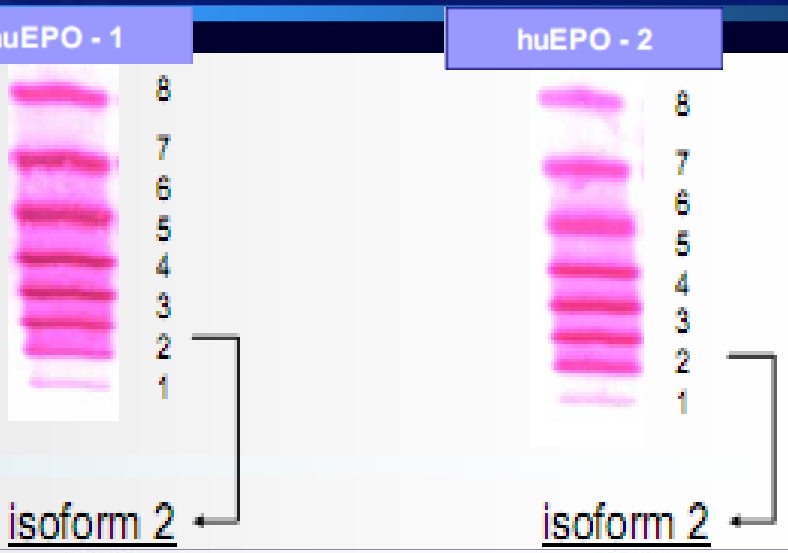




What looks almost same , may be different!

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Predictive Diagnostics & Cell Therapies

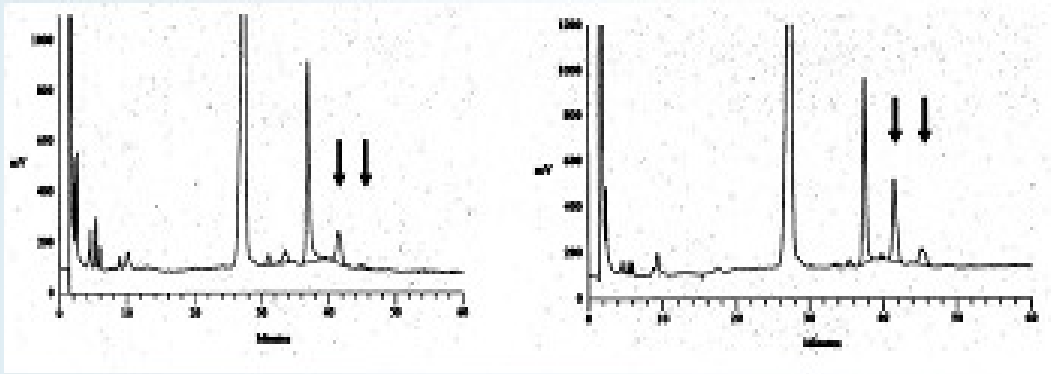
IEF pattern and sialic acid content of the two EPOs are very similar



… but the biological activity is very different

	huEPO - 1	huEPO - 2
Sialic acid	14.0	14.2
In-vivo activity (U/mg)	226,000	400,000

The carbohydrate structures of the two EPO isoforms are different



Adapted from Kresse
(Burg, J. et al. 1998 PCT/EP/98/07876)

Immunogenicity: impact on efficacy and safety

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Predictive Diagnostics & Cell Therapies

- If a Biological product is injected which is not the natural protein - immune system starts working to attack the foreign protein. This immune response can vary from no perceptible effect to significant clinical effects:
  - Generalized immune effects (allergy, anaphylaxis)
  - Neutralization of exogenous protein(loss or enhancement of drug efficacy)
  - Neutralization of the endogenous protein(serious adverse event)
- Factors influencing immunogenicity:
  - Amino-acid sequence, glycosylation, host cell impurities, formulation, handling/storage(aggregate formation)
  - Route of administration SC>IM>IV, concomitant disease, genetic factors.

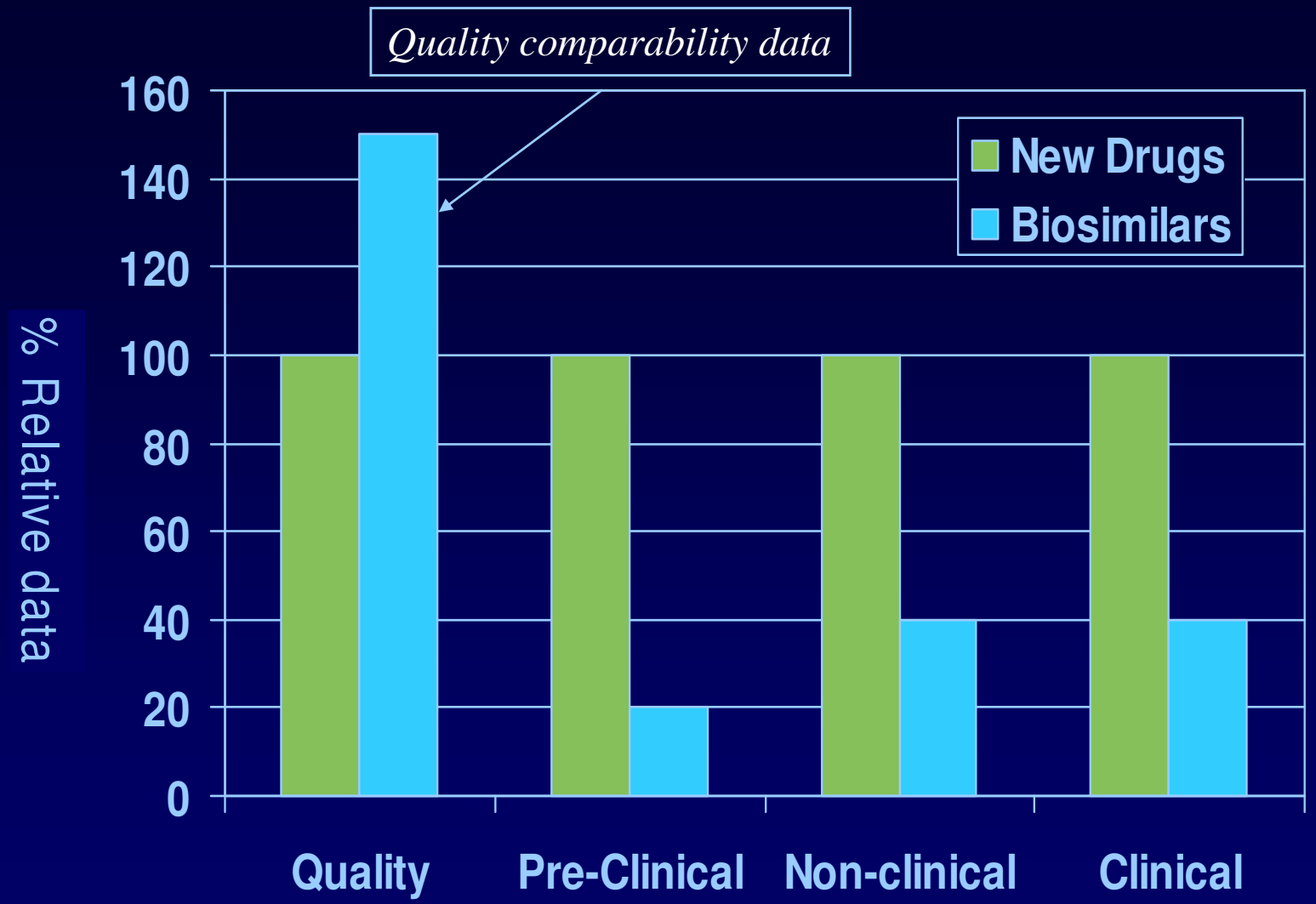
Immunogenicity: impact on efficacy and safety

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Predictive Diagnostics & Cell Therapies

- Biosimilars cannot be assumed to have the same immunogenicity profile as the original product.
- Because immunogenicity is largely unpredictable, the assessment of a biosimilar must be based on:
  - a thorough risk-benefit analysis
  - Robust post-marketing risk management programmes
- Physicians and hospital pharmacists should remain alert to unexplained changes in drug efficacy or side effects.

Comparability Concept for Biosimilars/Follow-ons

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Differences of Biosimilar/ Follow-on Products

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Known, detectable differences

- Genetic construct and cell line
- Cell culture/fermentation conditions
- Purification process and in-process controls
- Characterization test and specifications
- Micro heterogeneity for glycoforms
- Impurities and variants

Unknown, hard-to-detect differences

- Biological activities
- Structural/conformation
- Immunogenicity
- Efficacy/safety

Goals of Quality, Non-clinical, and Clinical Studies

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Predictive Diagnostics & Cell Therapies

Quality

- To demonstrate comparability of the product to a reference product- **the most critical step.**

Pre-clinical toxicology

- To confirm therapeutic index and safety profile.
- To qualify impurities by short-term animal studies .
- Full animal toxicity studies are not necessary.

Non-clinical PK/PD studies

- To confirm dosing regimen by PK profiles.
- To confirm the mechanism of actions by biomarkers (PD).

Clinical safety

- To compare immunogenicity and/or hypersensitivity with the reference products

Efficacy

- To conduct confirmatory clinical trials (smaller scale).
- Use of complementary biomarkers,or surrogate endpoints.

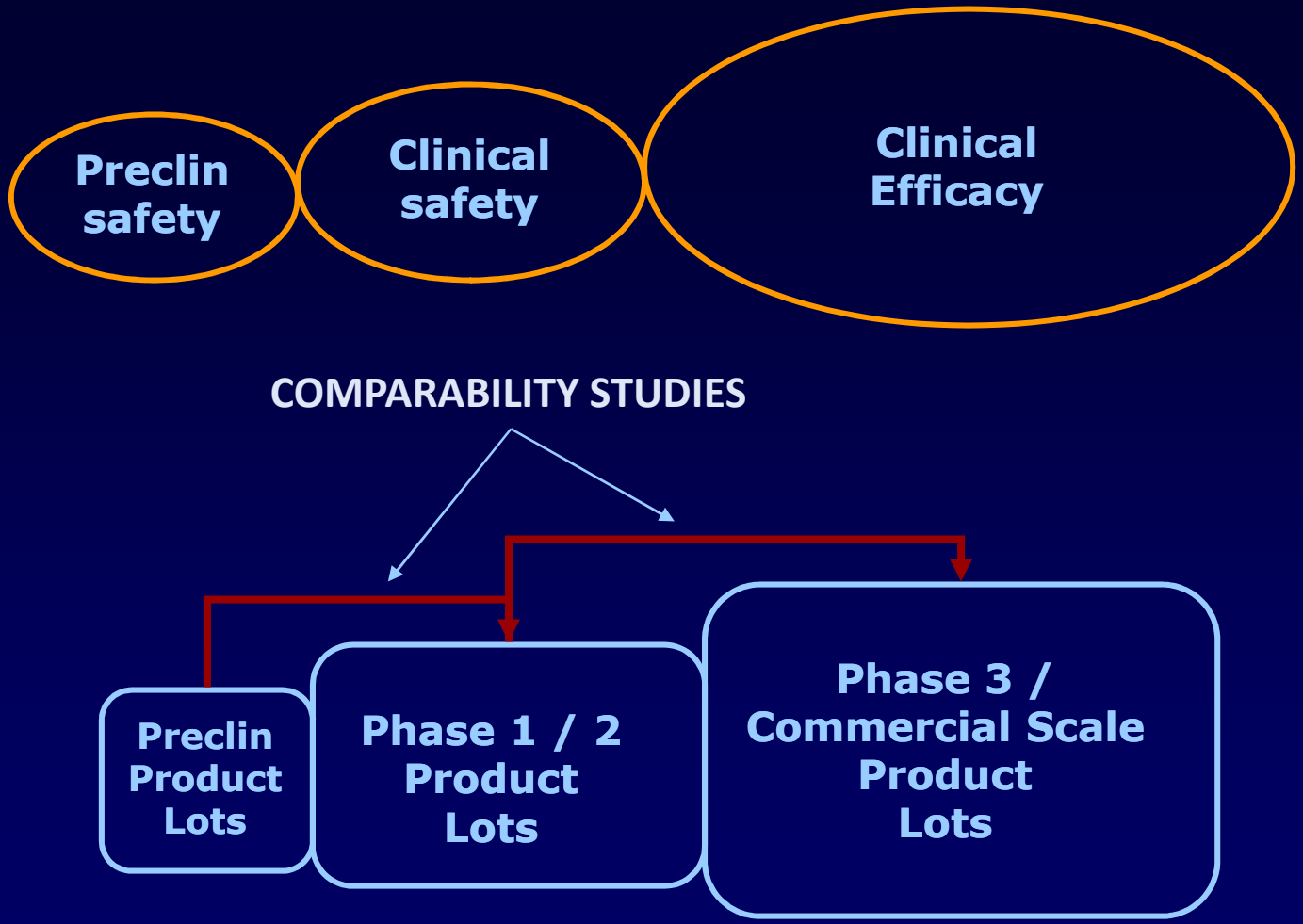
Major Challenges by Companies from Asia

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Predictive Diagnostics & Cell Therapies

- Regulatory requirements and patent issues.
- Cell line and process for manufacturing of products meeting comparability criteria.
- Capacity of manufacturing and compliance with internationally recognized GMP standards.
- Comparability issues after changes in site and scale.
- Product-specific issues on comparability testing.
- Ability to secure reference products for comparability testing including pre-clinical and clinical studies.
- Design of non-clinical and clinical studies that meet regulatory requirements.
- Development costs and competitions from 2nd generation products and bio-betters.

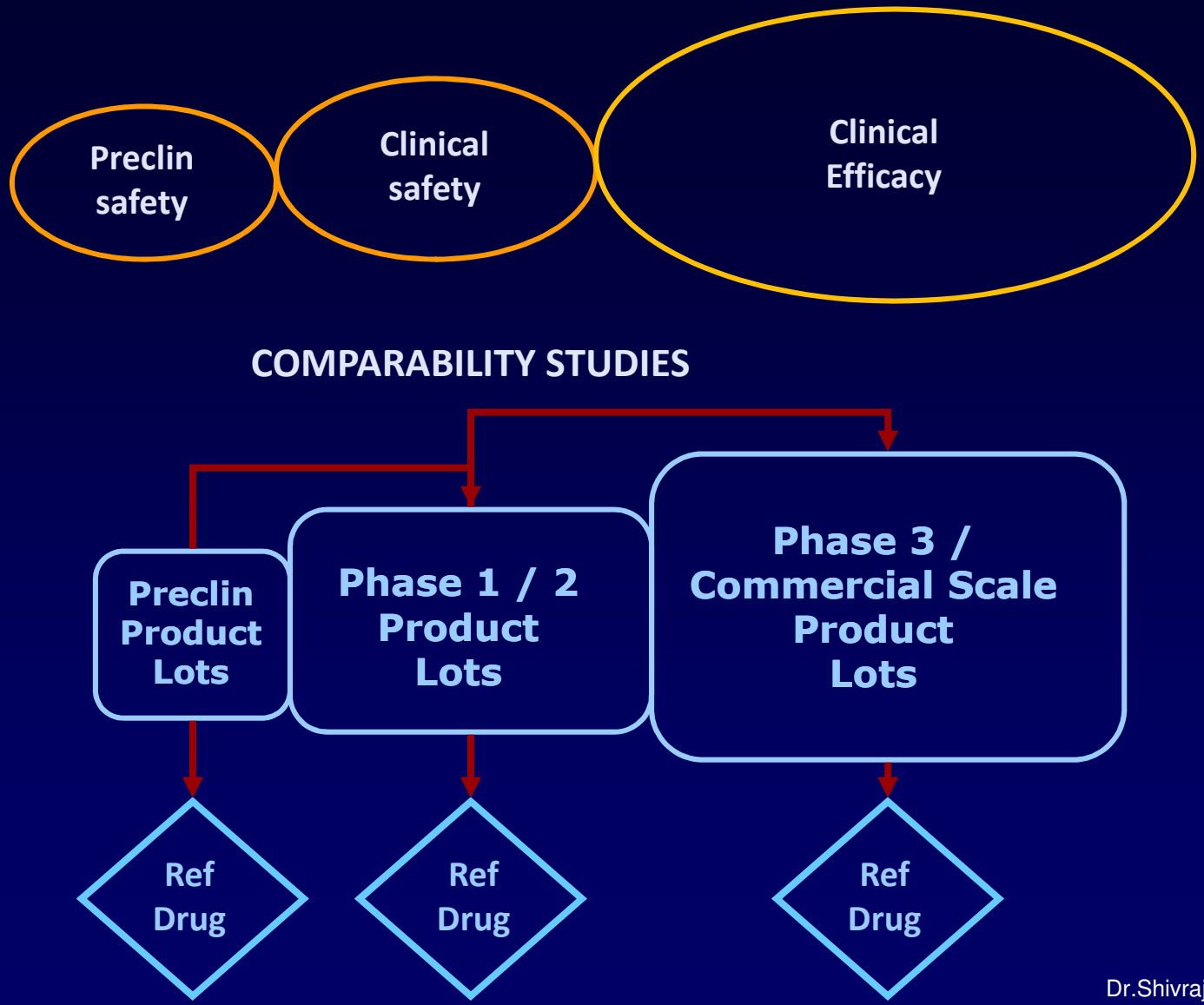
Comparability Paradigm – Innovator Product

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Predictive Diagnostics & Cell Therapies



Comparability Paradigm – Follow On Biologic (Biosimilar)

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Outstanding issues

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Pharmaco vigilance systems :

This is not an issue unique to biosimilars …..
existing issue that is highlighted and exaggerated by their arrival

Eprex® → Biosimilar EPO α (1) → Biosimilar EPO α (2) → *Adverse Event*

Ensure traceability

Company and Regulatory Agency AE reporting systems should distinguish one manufacturers product from another

- Complex, if biosimilars have the same INN as the innovator
- AE reports are often incomplete eg. lot number

Prevent repeated, uncontrolled substitution

Repeated, uncontrolled substitution will confound accurate pharmacovigilance

- Occasional changes are inevitable or necessary in chronic therapy

Substitution does not apply to Biosimilars

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Medicines are the same = therefore can be safely substituted

✓ Generics / chemical drugs

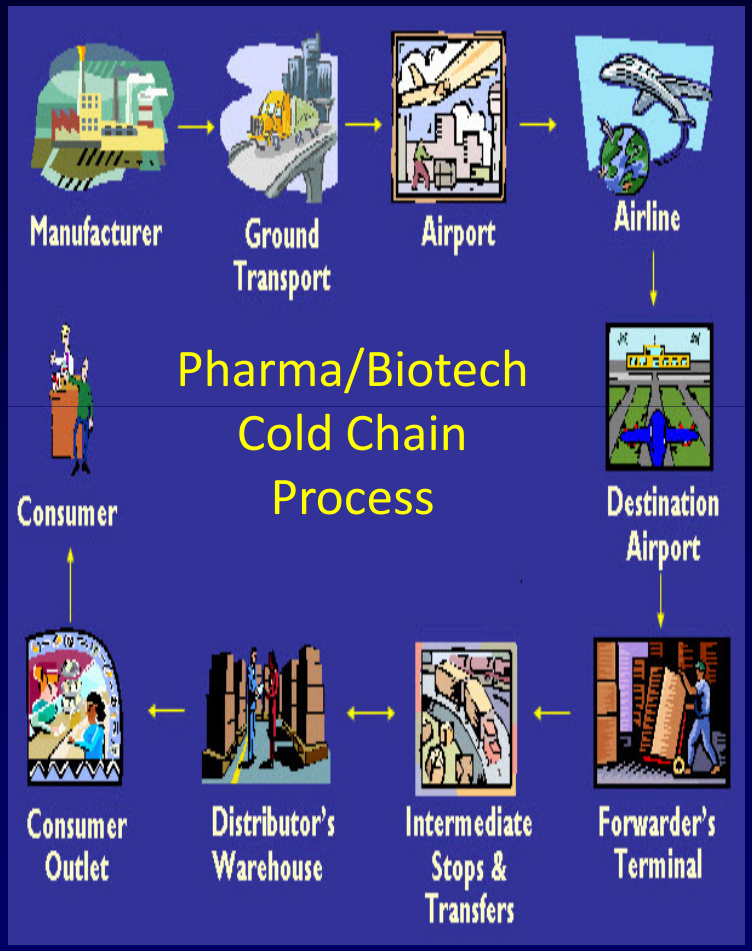
Substances are identical = therefore can be substituted

✗ Biosimilars/Biotech medicines are not identical

Can generic substitution rules be applied?

Therefore, with biotech medicines and biosimilars, the generic substitution rules do not apply

Creative supply Chain strategies ensures success



Worldwide sales of vaccines predicted to rise to $35 billion by 2014

Huge growth of temperature sensitive vaccines is driving the development of novel technologies for transportation and logistics such as thermo stable vaccines, solar “battery free” refrigerators, “zero energy” cold chain electric vehicles and longer-term passive storage containers.

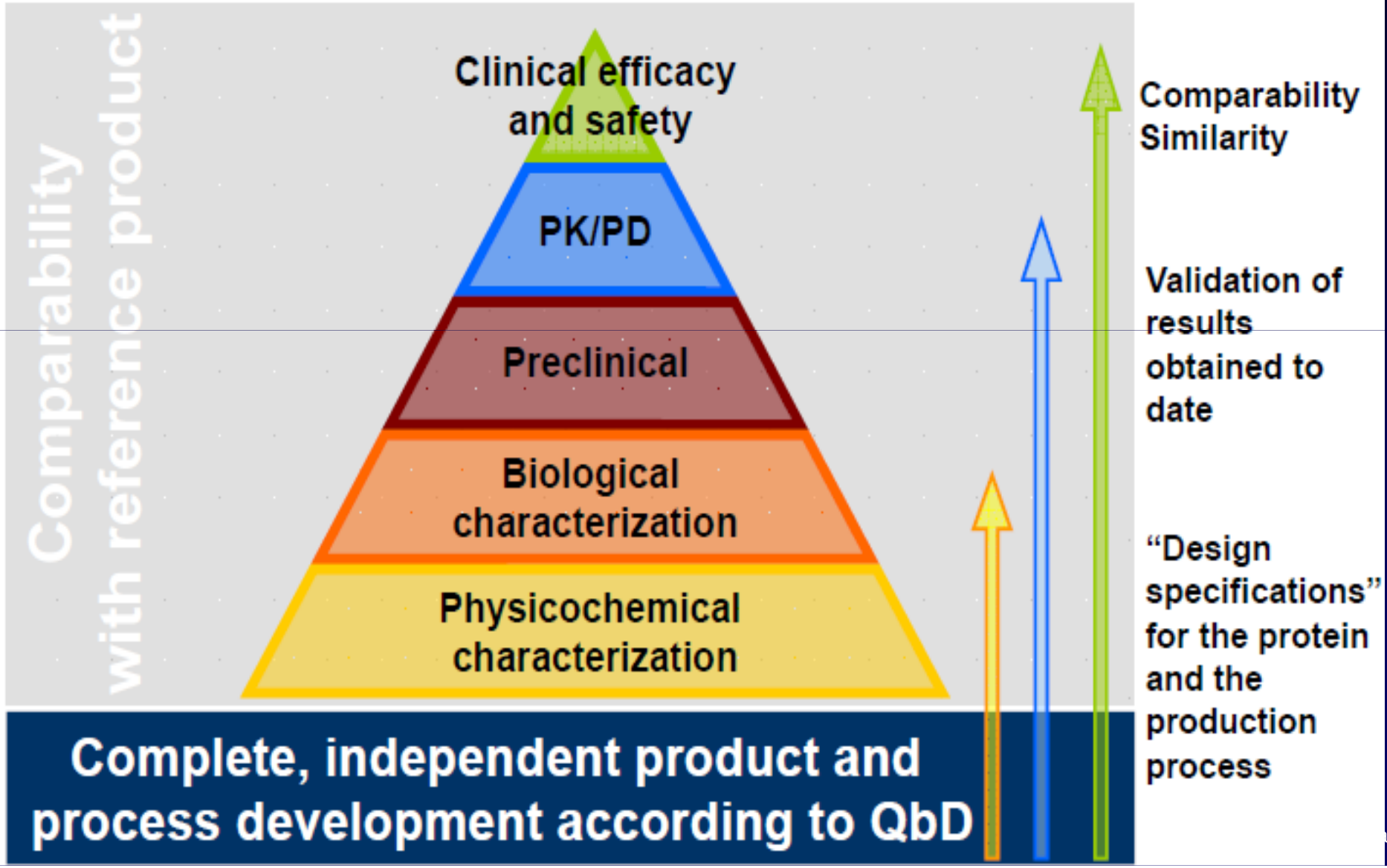
Development of sub-sectors such as biotech, medical devices, clinical trials and diagnostics are fuelled by high levels of innovation. leading to individual customer-centric solutions

India, with $ 2.36 bill. in biopharma market is set to become one of top 5 producers of biopharmaceuticals in the world by 2020.

“ The Comparability Exercise”

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Comparability with the reference product must be ensured at all levels.



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Biosimilar Regulation - ASEAN

Dr.Shivraj Dasari

HISTORY OF ASEAN

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Predictive Diagnostics & Cell Therapies

ASEAN – Association of Southeast Asian Nations

- 10 member countries

- Indonesia, Malaysia, Philippines, Singapore and Thailand (1967)
- Brunei Darussalam (1984)
- Vietnam (1995)
- Lao PDR and Myanmar (1997)
- Cambodia (1999)

Strengthening Regional Regulatory Frameworks through Partnership

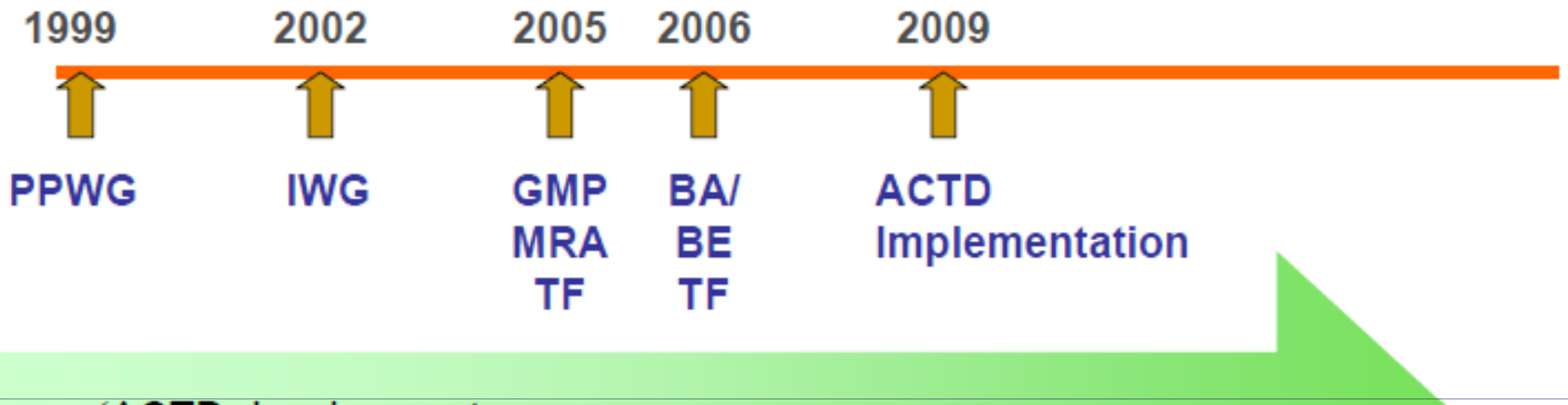
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Facts

- As of 2006, ASEAN region has a population of about 560 million
- Total area of 4.5 million square kilometers
- Combined gross domestic product almost US$ 1,100 billion
- Total trade of about US$ 1,400 billion

Harmonization Milestones



- ✓ACTD development
- ✓ACTR & technical guidelines development
- ✓Regulatory capacity building
- ✓Post-Market Alert System development
- ✓GMP Inspection MRA development
- ✓Training scheme development

- ✓ACTD implemented
- ✓ACTR & technical guidelines established (maintenance and enhancement of common interpretation ongoing)
- ✓Post-Market Alert System established
- GMP Inspection MRA finalized
- Training identified
- Pan-ASEAN registration

Back ground

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- 1992:
  - The ASEAN Consultative Committee for Standards and Quality (ACCSQ) formed to facilitate and complement the ASEAN Free Trade Area (AFTA).
- 1997
  - ASEAN regulatory bodies authorized to achieve mandate of eliminating technical barriers to trade.
- 1998
  - Efforts to harmonize regulatory requirements amongst ASEAN was initiated through the (ACCSQ)
- 1999
  - Concept of ASEAN pharmaceutical harmonization was presented by Malaysia and agreed upon by the Senior Economic Officials Meeting (SEOM)

ASEAN Consultative Committee for Standards & Quality /Pharmaceutical Product Working Group

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Pvt. Ltd. in Diagnostics & Cell Therapies

- 1992 AEM → ACCSQ → Working Groups (WGs)
  Product Working Groups (PWGs)
- 1998 ACCSQ → initiated the PPWG
- 1999 ACCSQ → endorsed the PPWG
- The Pharmaceutical Product Working Group (PPWG) was formed in 1999
  - Malaysia hosted the 1st PPWG meeting and was appointed the Chair and Thailand the Co-Chair.

Strategies

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- Comparative study on existing product registration requirements and regulations for pharmaceuticals
- Identification of key areas on requirements for harmonization
- Development of common technical requirements (CTR) for pharmaceutical product registration
- Development of common technical dossier (CTD) towards MRA
- Implementation of harmonized ASEAN Pharmaceutical Product Dossier by December 2008

Technical Cooperation

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- ACTR/ACTD
  - Quality – Indonesia
  - Safety – Philippines
  - Efficacy – Thailand
  - Administrative Data, Product Information and Glossary – Malaysia
- Guidelines
  - Analytical Validation – Thailand
  - Process Validation - Singapore
  - Stability Studies – Indonesia
  - BA/BE Studies - Malaysia

ASEAN Harmonized Product

- ASEAN Common Technical Requirements and Dossier (ACTR/ACTD) on Quality, Safety and Efficacy plus Administrative Data and Glossary
- Guidelines on
  - Analytical and Process Validation
  - Stability Studies
  - Bioavailability/Bioequivalence

Impact of Harmonization

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- Public Health - Improve Quality, Safety & Efficacy
- Patients & Consumers - Improve access & availability
- Industry - Improve compliance to GMP, GSP, GCP, GLP
- Regulatory - Confidence building & Mutual understanding

ACTR

A set of Written Materials *intended to guide applicants to prepare application dossiers* in a way that is consistent with the expectations of all ASEAN Drug Regulatory Authorities

ACTD

The part of marketing authorization application dossier that is common to all ASEAN member countries

Content of ACTR - Quality

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Drug Substance

- - General info.
- - Characterisation
- - Ref. Std. or Materials
- - Stability
- - Manufacture
- - Control of Drug Substance
- - Container Closure System

Drug Product

- - Description and Composition
- - Manufacture
- - Control of Finished Product
- - Container Closure System
- - Pharmaceutical Dev.
- - Control of Excipients
- - Ref. Std. or Material
- - Stability
- - Product Interchangeability/Equivalence evidence

Contents of ACTR - Safety

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Pharmacology
- Primary P'dynamics
- Secondary P'dynamics
- Safety P'cology
- Drug Interaction

Toxicology
- Single Dose Toxicity
- Repeat Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive & Development Toxicity

Pharmacokinetics
Local Tolerance
Other Toxicity Studies
List of Key Literature Ref.

Contents of ACTR – Clinical Data

- BA & BE Studies
- Studies pertinent to P'cokinetics
- Human P'cokinetic studies
- Human P'codynamic studies
- Efficacy and safety
- Post marketing data (if available)
- References

Technical guidelines to ACTR - Quality

- Adopted the WHO's Guidelines
- Adopted the existing International Pharmacopoeia
- Adopted ICH-Quality Guideline (12GL's)
- Drafted 4 ASEAN Quality GL's
  - -Analytical Validation guideline
  - -BA/BE studies guideline
  - -Process Validation guideline
  - -Stability studies guideline

Technical guidelines to ACTR

SLS Cell Cure Technologies
Predictive Diagnostics & Cell Therapies

Safety

-adopted 15 ICH – safety guidelines

Efficacy

-adopted 11 ICH – efficacy Guidelines
(E1,E2A,E2C,E3, E4, E6-E11)

-adopted as Ref.Guidelines. 4 ICH – Efficacy Guidelines
(E2C(A), E2D, E2E, E12A)

-not adopted 2ICH – Efficacy Guidelines
(E2B(M), E5)

Contents of ACTD

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Predictive Diagnostics & Cell Therapies

- Part 1: ToC Adm.Data & Prod. Info.
- Section A: Introduction
- Section B: Overall ACTD-ToC
- Section C: Doc. reqd for Registration

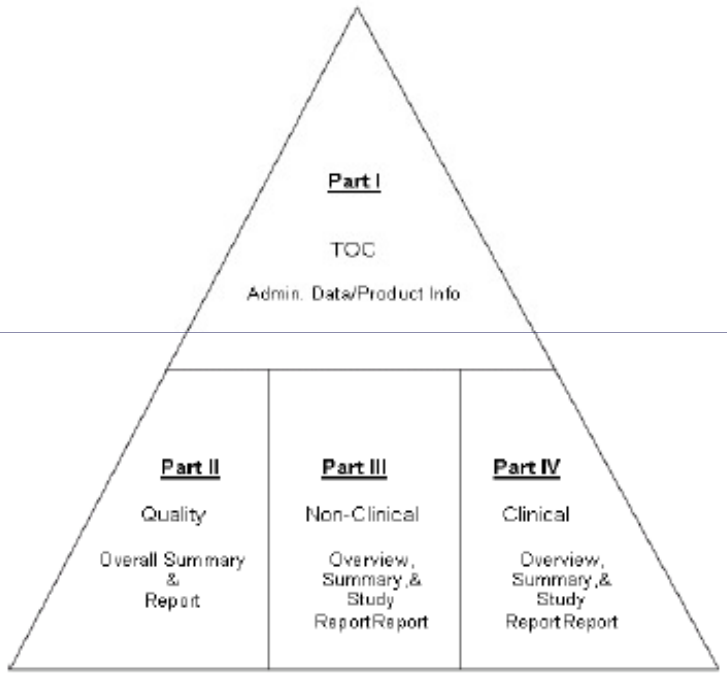
- Part 2 : Quality Document
- Section A: ToC
- Section B: Quality Overall Summary
- Section C: Body of Data

Note:
ToC = Table of Content
* = Upon REQUEST

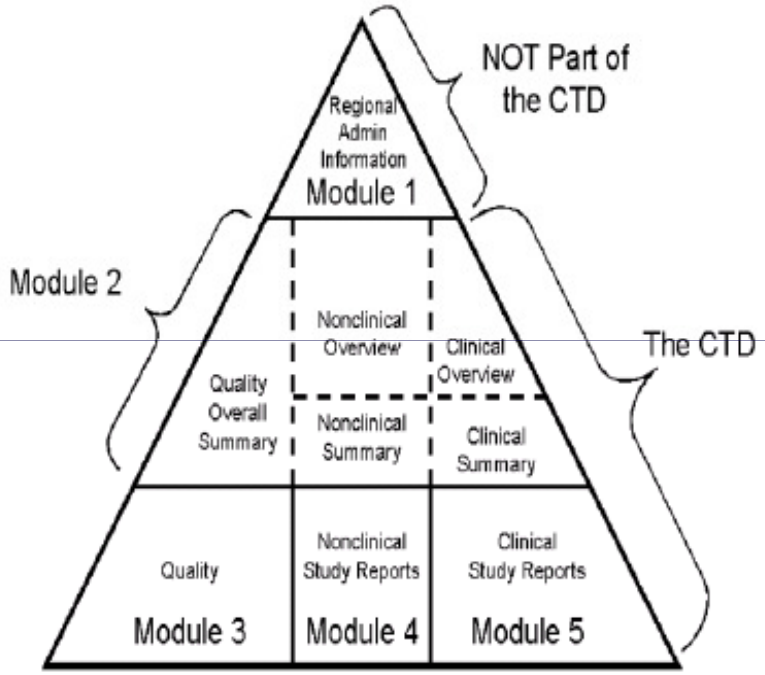
- Part 3 : Non-clinical / Safety Doc
- Section A: ToC
- Section B: Non-clinical Overview
- Section C: Non-clinical Written & Tabulated Summaries
- Section D: Non-clinical Study Reports*

- Part 4 : Clinical / Efficacy Doc
- Section A: ToC
- Section B: Clinical Overview
- Section C: Clinical Summaries
- Section D: Tabular Listing of All Clinical Studies
- Section E: Clinical Study Reports*
- Section F: List of Key Literature References

Organization of ACTD vs ICH -CTD



ASEAN-CTD



ICH-CTD

Main differences are the organization of data and the numbering of sections.

Implementation of A-CTD in the ASEAN region is planned on 31 Dec 2008

Current Status

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Country	Full Implementation Date	Products (country info)	Current situation
SINGAPOUR*	31 Dec 2005	Pharma / Bio	Full implementation
MALAYSIA*	31 Dec 2005	Pharma	Full implementation
INDONESIA*	1 Jan 2008	Pharma	Draft ACTD
VIETNAM	31 Dec 2007	Pharma	Draft ACTD currently in review
THAILAND*	31 Dec 2007	Pharma / Bio	ACTD for biologicals currently in review
CAMBODIA	31 Dec 2008	-	Initiated the implementation of part I
LAO PDR	31 Dec 2008	-	Initiated the implementation of parts I and II
MYANMAR	-	-	Plans to implement are underway
PHILIPPINES*	31 Dec 2008	Pharma	Initiated in Jan 2005
BRUNEI	31 Dec 2008	-	Parts I & II implemented

Implementation of ACTD

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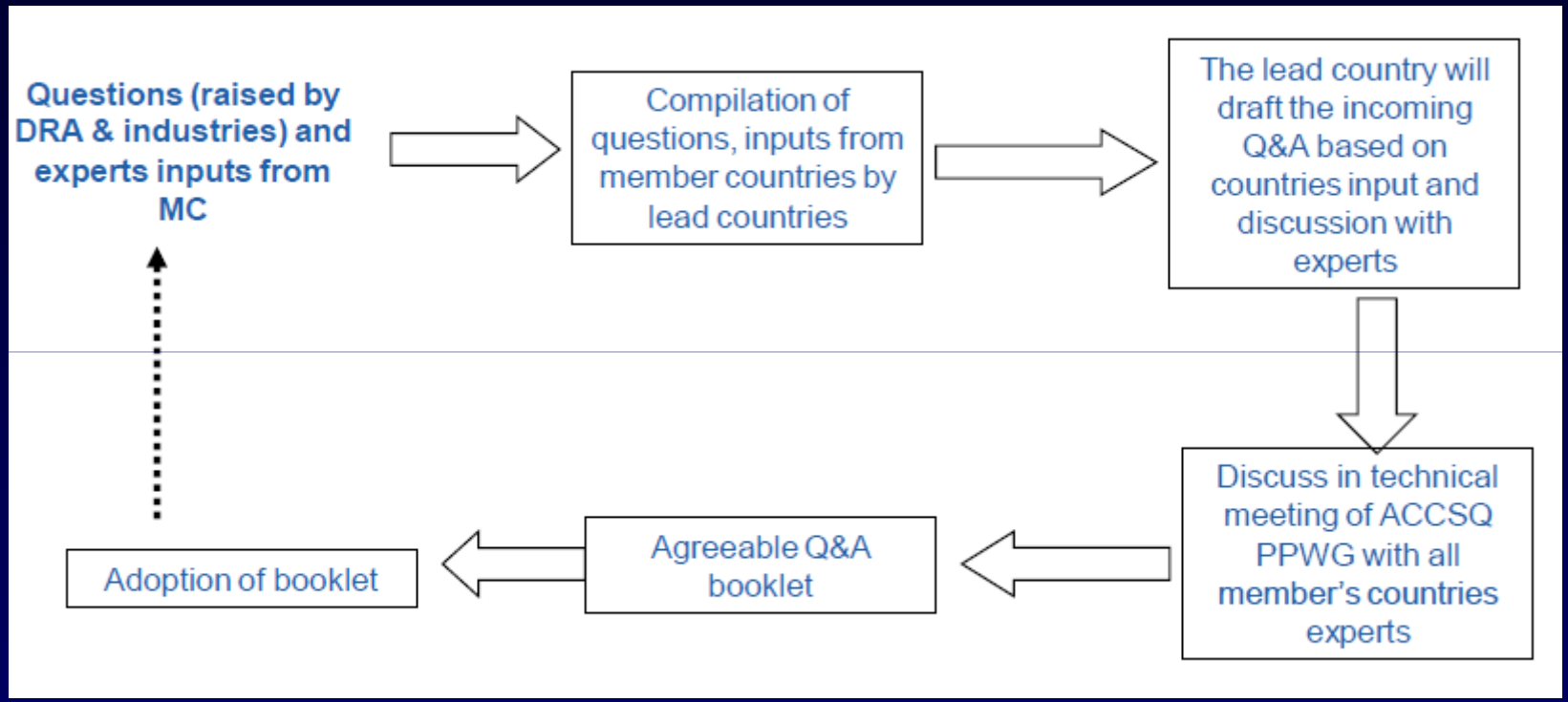
Full implementation after 31st Dec 2008

- 12th ACCSQ PPWG meeting: ICH format is still acceptable after 1st Jan 2009.

Flexibility to use ICH-CTD format for:

- Innovative therapeutic products(NCE)
- Biological & biotechnical products -> vaccines.

How is it going to work?



Additional requirements for ASEAN countries - Singapore

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Special Documents requested:

- Appendix 8 : Singapore QOS for Biologic
- Validation sheet
- Singapore Stability Sheet

Stability requirements different from ICH, valid for NCE's (not for NBE's):

- Long term testing:

-Products packed in semi-permeable containers:30^0 C$\pm$ 2^0C/75% RH$\pm$5% RH – min.12 months.

-30^0C $\pm$ 2^0C, humidity not specified (for products in impermeable containers), 12 months

- Accelerated studies: 40^0C $\pm$ 2^0C /75% RH $\pm$ 5% RH – min 6 months
- Stress studies : 40^0C $\pm$ 2^0C /75% RH $\pm$ 5% RH.

ASEAN – Stability guideline implementation

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Stability requirements different from ICH:

- 30^0 C + 2^0C / 75% RH + 5% RH – 0,3,6,9,12,18,24 months
- 40^0C + 2^0C / 75% RH + 5% RH – 0,3,6,months
- Reviewed by 14th ACCSQ-PWG in Feb 2008.
- Full implementation planned for January 1st 2009.
- No transition period foreseen
- Requested for all products (also retrospectively)

CONCEPT OF AN MRA

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Definition

- Theoretically an MRA is a treaty signed between Governments of all Member Countries.

Objective

- To implement a harmonized pharmaceutical regulatory scheme.
- For the products subjected to product registration approval, the sectoral MRA would allow them to be marketed in the other ASEAN countries if the product have been registered accordingly in one ASEAN country

Sectoral MRA on GMP inspection

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Each National Drug Regulatory Authority (NDRA) proposes an Inspection Service, which is responsible for :

- Inspecting manufacturers of medicinal products
- Issuing a GMP inspection report

This GMP inspection report can be requested by other NDRAs and ne mutually recognized in the ASEAN countries.

Sectoral MRA on GMP inspection

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Benefits

- Avoidance of duplication of GMP audits among ASEAN Member Countries
- Savings on time, resources and cost for both regulators and industry
- Facilitation of trade and export
- Quicker access of medicinal products to patients across ASEAN

Signed during the 13th PPWG Meeting in April 2008.

ASEAN Post –Marketing Alert System(PMAS)

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Lead Countries : Singapore & Malaysia

Objective

- Share information relating to defective or unsafe product/pharmaceutical product
- Major safety concerns can be acted upon in timely manner

In the event of a major safety concern that results in a recall or withdrawl, the PMA system cane be used to notify the various regulatory agency in a timely manner

- A Singapore PMAS pilot scheme was launched in April 2005
- ASEAN PMA system adopted in Feb 2006 by all the ASEAN members.

Process & Communication

A PMAS coordinator is named in each Member Country(MC)

He is responsible for

- Validating the information
- Sending an alert notification to other member countries (Standardized ASEAN reporting form)

A MC receiving the alert may then wish to follow up the original MC for further information, clarification or necessary regulatory action on an individual basis.

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Perspectives

SHORT TERM PERSPECTIVES

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2008-2009

- 1 Dossier for the entire ASEAN region but 1 submission in each member country
- Harmonization of packaging/labeling requirements

Common Variation Guidelines

- Across the ASEAN region, changes to approved dossier are handled as a variation or a new registration.
- Need to harmonize
- Proposed basis: guidelines from Singapore or Malaysia

New ACTR and <<technical>> MRA to harmonize the ASEAN region?

Mid and long term perspectives

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2008-2012: Pan ASEAN Registration

- MRA for Product Registration
- Allow products tested and assessed in 1 ASEAN country to be marketed in other ASEAN countries, without repeating the testing and certification processes
- Quicker product registration & improve intra ASEAN trade

- Post 2012 : Towards a centralized and decentralized procedures

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Challanges

Greatest Challenges

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- Gaps in the training and level of expertise between developed countries and developing ones
- Lack of competency for regulatory officials as well as for regulatory personnel of the pharmaceutical companies (especially on vaccines, Biopharmaceuticals)
- Different approaches and understanding of concepts among national authorities
- ACCSQ is developing a <<mechanism to monitor the Implementation of ASEAN policy guideline>>

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SLS Cell Cure Technologies Private Limited, Flat 103, Prabhat Apartments, Street No.11,
Secunderabad-500026., A.P. India., Tel/Fax: +91-40-27734415.,
email:shivraj23@yahoo.com.,www.slscellcure.in



SLS Cell Cure Technologies Pvt.Ltd.,
Flat-103, Prabhat Apartments. East Marredpally,
Secunderabad-500026, A.P; Tel:+91-40-27734415; Fax:+91-40-27734415.
URL:slscellcure.in. email:shivraj23@yahoo.com