

## ISPOR 6th Asia-Pacific Conference - 2014

### Workshop 07:

## USING WEIGHTED CRITERIA FOR MAKING DECISIONS ON OFF-PATENT MEDICINES: CASE STUDIES FROM CHINA, THAILAND, AND VIETNAM

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**Diana BRIXNER**, PhD, RPh, Professor & Executive Director, Department of Pharmacotherapy, University of Utah, Salt Lake City, UT, USA;

### Using weighted criteria for making reimbursement decisions for off-patent pharmaceuticals in China, Thailand and Vietnam

- Introduction of Faculty, Agenda D. Brixner
- Use of weighted criteria for decision making for generics D. Brixner
  
- Implementation of multi-criteria decision process for tender decisions in Beijing (China) SL Hu
- Analysis of using MC in pharmaceutical price setting (China) SL Hu
- Decisions for the Essential Drug List (Thailand) S Ngorsuraches
- Quality of pharmaceutical products and the classification of products for tender (Vietnam) J. Shen
- Discussion D. Brixner

## Agenda

- Introduction of Faculty, Agenda D. Brixner
- Issues with current approach to decision making D. Brixner
- Proposing decision criteria

### **Diana Brixner, PhD, RPh**

Professor and Chair, Department of Pharmacotherapy  
Executive Director Outcomes Research Center  
College of Pharmacy

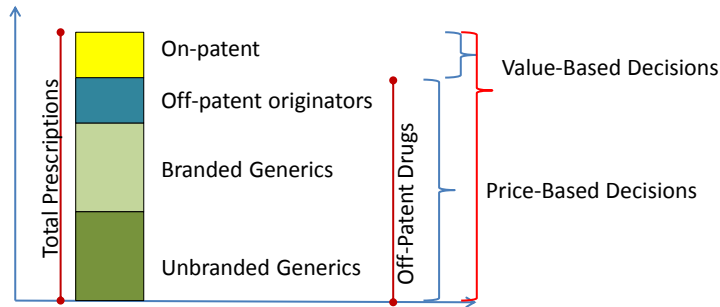
Director of Outcomes  
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## Use of weighted criteria for decision making for generics

- Making value decisions in branded vs. generic drugs
- Proposed weighted criteria to assist in these decisions
- Examples of weighted criteria
  - Bioavailability
  - Outcomes evidence
  - Quality control
  - Drug shortage prevention
- Policy implications

## Should price be the only criterion when making therapeutic decisions for the majority of patients?



- » Including all off-patent products, it can be assumed, that over 80% of patients are treated with off-patent drugs (*Originators, Branded Generics, INN Generics*)
- » After patent loss, decisions are increasingly based on price

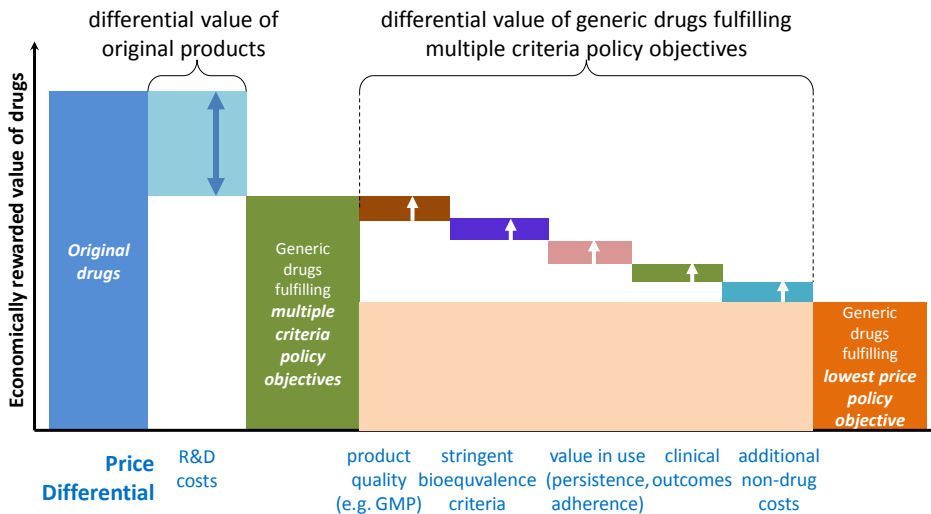
INN = International Non-proprietary Name

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## Economical value of generic drugs (or drug policies?)



\* Kaló Z et al. submitted to Value in Health 2014

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## Multiple criteria to be considered when deciding on off-patent medicines

1. Proof of pharmaceutical equivalence
2. Proof of bio-equivalence
3. Differences in formulations, excipients and process technology
4. Effect on patient adherence
5. GMP (*Good Manufacturing Practice*) and Quality standard
6. Supply reliability
7. Added value (*e.g. Disease/ patient educational services, disease outcome solutions*)
8. Stakeholder partnership (*e.g. Public-private-partnership on local health care infrastructure and expertise build-up*)
9. Local investment (*e.g. manufacturing, R&D, employment*)
10. Other according to local policy priorities (*work conditions & benefits, environmental standards etc.*)

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## International Definitions of a „Generic Drug“

WHO

... “is a pharmaceutical product, usually intended to be **interchangeable** with an **innovator product**, that is manufactured without a license from the innovator company and **marketed after the expiry date of the patent or other exclusive rights.**”

FDA

“...is the **same** as a **brand name drug** in dosage, safety, strength, how it is taken, quality, performance, and intended use.”

EMA

„A medicinal product which has the **same qualitative and quantitative composition** in active substances and the same pharmaceutical form as the **reference medicinal product**, and whose **bioequivalence** with the reference medicinal product has been demonstrated by appropriate **bioavailability studies**“

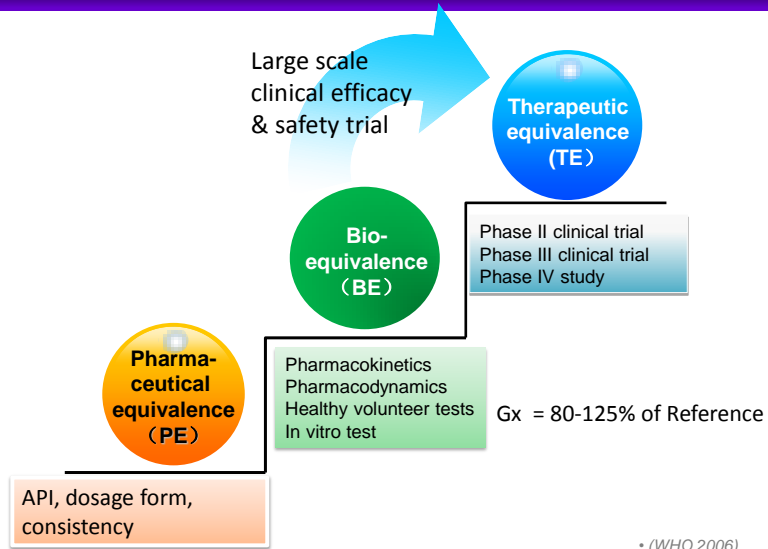
• Alfonso et al. – submitted to AHEHP. Alfonso et al, ISPOR 2013 Buenos Aires

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# Interchangeability? Different Equivalence Tests



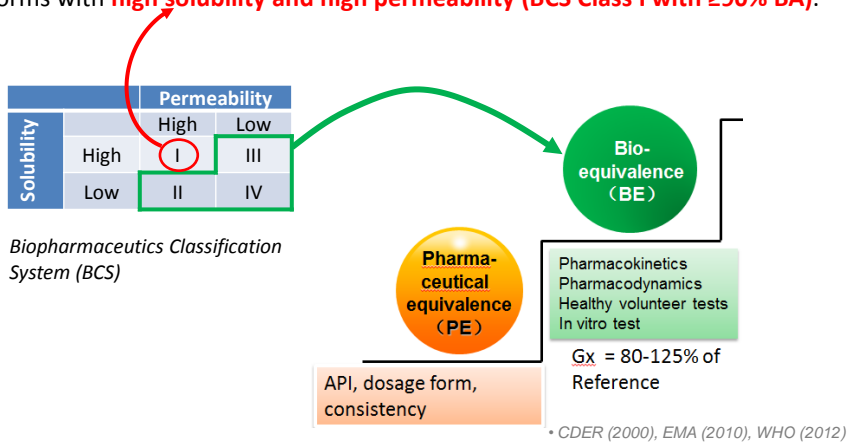
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# Should bio-equivalence study be exempted?

Bio-equivalence studies can be waived for immediate release oral dosage forms with **high solubility and high permeability (BCS Class I with ≥90% BA)**.



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## Limited evidence on the impact of generics policies

A Systematic Review

# The Impact of Generic Substitution on Health Outcomes and Costs

Imke **Schall**, Bakk, Diana **Brixner**, RPh, PhD

Kim **Saverno**, PhD, RPh, Martina **Mitrovic**, Mag., Agnes **Luzak**, MPH, Holger **Gothe**, MD, Uwe **Siebert**, MD, MPH, MSc, ScD <sup>1</sup>,

Institute of Public Health, Medical Decision Making and Health Technology Assessment; Department of Public Health and Health Technology Assessment,

**UMIT – Univ. Health Sciences, Medical Informatics and Technology**, Eduard Wallnoefer Center I, A-6060 Hall i.T., Austria

### Poster PHP 28



Schall I, Saverno K, Luzak M, Brixner D, Schall K, Saverno A, Luzak M, et al. The Impact of Generic Substitution on Health Outcomes and Costs: A Systematic Review. ISPOR 16th Annual European Congress, 2013. *Value in Health*. Dublin: International Society of Pharmacoeconomics and Outcomes Research; 2013. p. Poster PHP28

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## Systematic Review: Background and Objectives

- Generic substitution of branded drugs is often mandated by government and other health care payers in order to reduce healthcare expenditures.
- The premise of bioequivalence has not been tested against the same standards of clinical and economic outcomes as the branded counterparts
- Tested hypotheses
  - generics and branded products yield the same health outcomes
  - generic therapies save economic resources versus branded therapies

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# Systematic Review: Search Results

## 40 Studies included

- 32 ⇨ **clinical** outcomes **only**
- 3 ⇨ **economic** outcomes **only**
- 4 ⇨ **economic AND clinical** outcomes
- 14 studies on de novo patients
- 24 studies on maintenance therapy
- 2 studies relating to both

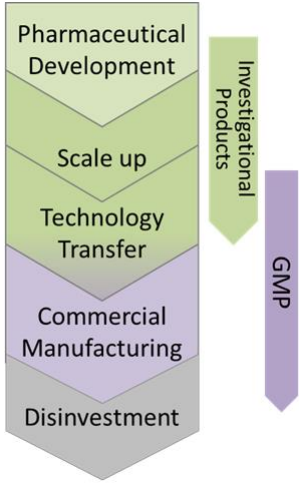
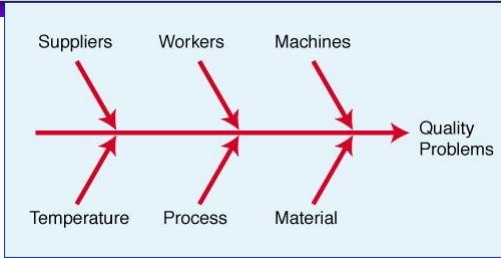
Study Countries	
Austria	Netherlands
Canada	Philippines
Germany	Poland
India	Slovenia
Israel	Sweden
Japan	Taiwan
Korea	Thailand
Malaysia	USA

Therapeutic Categories
Anti-Epileptic Drugs
Anti-arrythmics
Anti-coagulants
Anti-hypercholesterolemics
Anti-hypertensives
Anti-psychotics
Ocular (glaucoma)
Immunosuppressives
Oncology
Osteoporosis

# Systematic Review: Results

- 66% of the outcome comparisons reported similar clinical outcomes for generic and original brand drugs
  - Hypothesis 1 (similar clinical outcomes) was largely supported
- 64% suggested that brand products had lower costs compared to generic substitution.
  - Hypothesis 2 (generic drugs save money) was largely rejected.

# Importance of Quality Assurance and Quality Control



- Detailed knowledge of the product and processes are essential.
- Throughout the entire product development
- All contribute to the overall product quality

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# Drug shortages. It is about patients getting the right therapy when they need it

## Nutritional Drug Shortages Take Toll on The Smallest Patients



2-year-old Finley Owens relies almost entirely on intravenous nutrition. (Courtesy Nicole Gemdt)

By GILLIAN MOHNEY  
June 14, 2013

## Cardiology today

**Record-high drug shortages threaten patient health and safety**

Cardiology Today, December 2011

Drug shortages in the United States, which reached record highs in 2010, continue to vex physicians, patients and manufacturers. Although affecting all medical specialties, the effects of drug shortages have been felt most acutely in oncology, emergency medicine, anesthesia and cardiology, significantly affecting patient care.

**Drug shortage leads to cancer relapse in patients in Singapore**

**Singapore:** Drug shortage is linked to higher rate of relapse among children, teenagers and young adults with Hodgkin lymphoma enrolled in a national clinical trial, according to research led by St Jude Children's Research Hospital.

**India urged to act on TB drug shortage**

The humanitarian aid group, Médecins Sans Frontières, says the Indian government has to act now to tackle a crisis in the public health system.

Updated 19 June 2013, 18:30 AEST

**PAPUA NEW GUINEA: Drug shortages put patients at risk**

PORT MORESBY, 26 February 2009

The country's finest hospital has been in dire need of medical supplies for more than a month, with the head of surgery, Ikau Kevau, expressing concern about the shortages of syringes, catheters and essential drugs in operating theatres

8. Sep. 2011

**CHINADAILY ASIA**

Home News Business Opinion Focus Life Sports Special Photo Vid

Home > News

Wednesday, January 8, 2014, 11:09

**Health agency to tackle drug shortage**

By Shan Juan

Treatment for hyperthyroidism gets harder to find as profits shrink

The top health authority vowed to introduce a solution to the shortage of drugs for patients who suffer from hyperthyroidism in China.

In early 2013, Chinese patients with hyperthyroidism began reporting problems in procuring their medication, widely known as Tapazole.

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# Policy Discussion Article



## Consideration of international generic distribution policies on patient outcomes in the United States and Germany

**Authors:** Saverno, K.; Gothe, H.; Schuessel, K.; Biskupiak, J.; Schulz, M.; Siebert, U.; Brixner, D.

- Generic substitution of narrow therapeutic index drugs can have unintended consequences.
- Generic switching is often driven by cost incentives, regulations and supply, but may raise concerns about:
  - equal bioavailability
  - therapeutic equivalence and about possible
  - confusion for the patient
- Warfarin was associated with poorer outcomes when switching occurred and that the US and Germany both have policies to purchase the least expensive generic on a periodic basis.

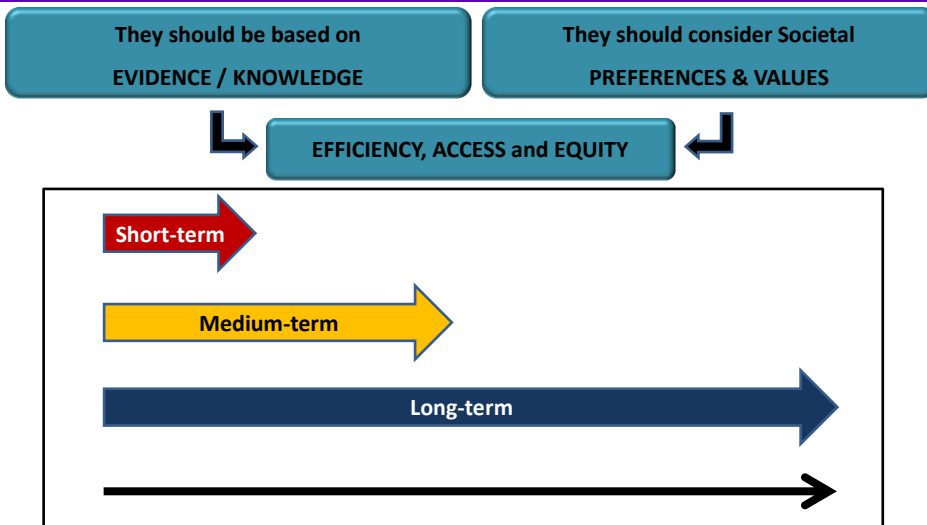
Source: [Die Pharmazie - An International Journal of Pharmaceutical Sciences](#), Volume 69, Number 3, March 2014, pp. 238-240(3)

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# How should Drug Policies be designed?

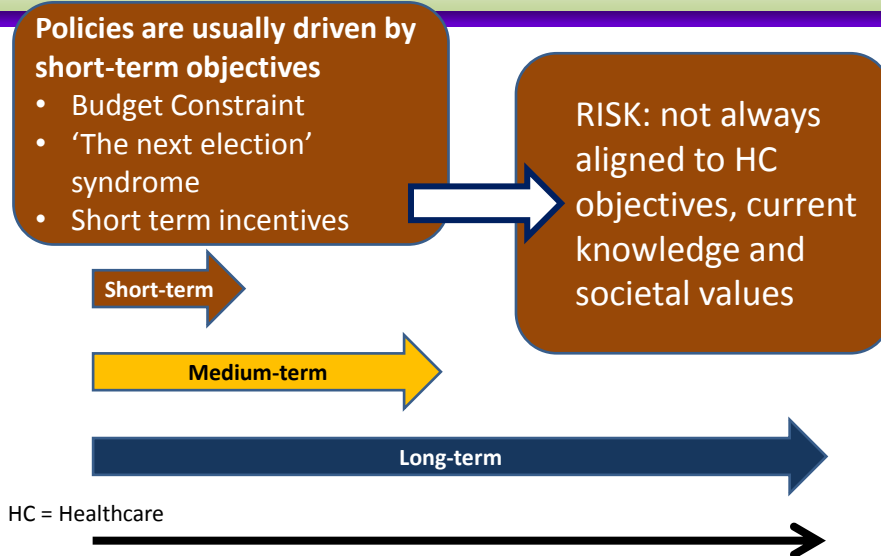


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## Reality of Many Current Drug Policies

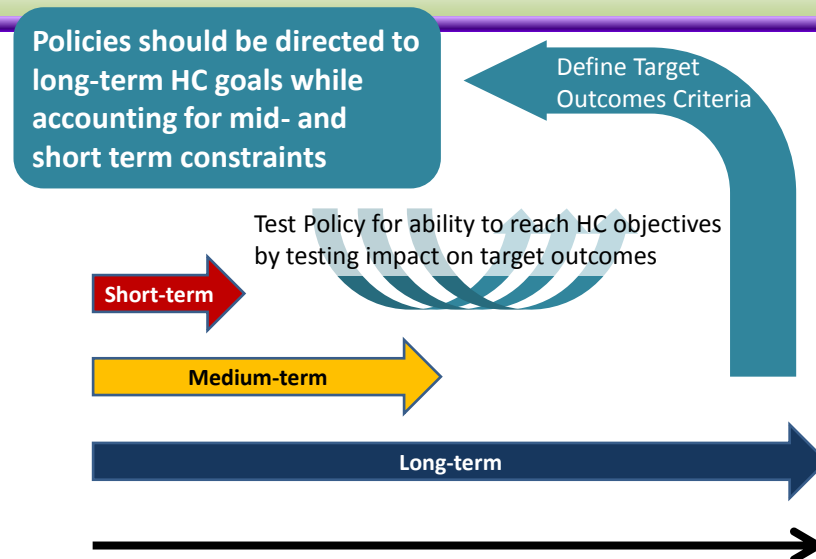


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## Process for Designing Drug Policies



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2014-2016 Chair, ISPOR Asia Consortium Health Technology Assessment Agencies,  
Health Care Policymakers & Payers (HTA & Policymakers) Committee

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## MC for tender decisions in Beijing (China) The issue and objective

- Current tendering systems only consider drug prices rather than the quality
  - ⇒ price lower than the production cost; finally
  - ⇒ manufacturer unable to produce drugs; will be out of stock
- There are no standardized bidding procedures, such as the separation of bidding between essential medicines and non-essential medicines,
  - ⇒ the bidding is not related with purchasing
  - ⇒ the price of procurement is not linked to volume
- What is the rational relative importance of economic & technical indicators (quality) and commercial indicators (price)?
- **The objective is to summarize the experience of tender decisions in Beijing and other provinces in China**

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## MC for tender decisions in Beijing (China) The political process - why a MC process?

- All reformed public hospitals will eliminate the drug mark-up, drug sale will no longer be as a part of hospital revenue
- The drug procurement in all hospitals will go through provincial bidding platform, i.e., conducting integration between bidding & purchasing, volume-based pricing and “two envelope system”
- Classified management: Low price drugs, exclusivity drugs, special drugs and price competition drugs
  - On-Patent / originals
  - Off-patent drugs
  - Individual pricing drugs
  - High quality products (premium price)
  - National innovative drug
  - Confidential traditional Chinese medicines\*
  - Drugs passing the new GMP criteria
  - With FDA or EMA certification
- Stratified bidding by drug quality uses multiple criteria

*\* non-disclosure of the components (ingredients)*

## MC for tender decisions in Beijing (China) The MC process and the weighting

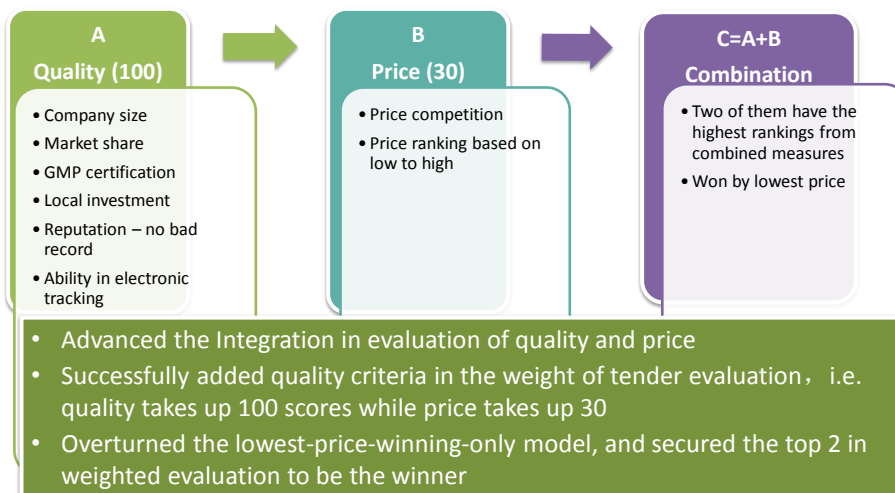
### BJ Tender Criteria Transformation

	Evaluation Item	Scoring	Weight (%)
Manufacturer Size (50)	1. Quality Assurance (GMP)	3	3.0
	2. Company Rankings in China (per MIIT)	10	10.0
	3. Annual Turnover (revenue V.A.T)	15	15.0
	4. Innovation (as recognized in China)	12	12.0
	5. Local investment and contribution	5	5.0
	6. Corporate Brand ( Subjective scores )	5	5.0
Product Quality (50)	7. Quality Specification	5	5.0
	8. Differential Pricing (per NDRC)	10	10.0
	9. Product line/formulation quality control(GMP)	5	5.0
	10. Tender winning record	10	10.0
	11. API Quality Control (GMP)	2	2.0
	12. Output Ranking ( per MIIT)	10	10.0
	13. Electronic Monitoring	3	3.0
	14. Product Reputation ( Subjective scores )	5	5.0
Additional Point (10)	15. Bad Records of Quality (Negative)	-10	
Total		100	100

Subjective Scores will be determined by KOLs

## MC for tender decisions in Beijing (China) Implementation of the MC process

### Improved Beijing Tender Model



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## MC for tender decisions in Beijing (China) Experiences

- Integrated bidding system for both essential and non-essential medicines, hospital and grassroots health centers
- Establishing rational multiple criteria in bidding system: economic & technical criteria (60 % of scoring), commercial criteria (40 % of scoring)
- Reducing the mark-up rate in distribution process (3%-5% of total value of procurement) and only allow to issue two financial receipts (1.) distributor pay to manufacturer, 2.) hospital pay to distributor)
- Further price negotiation with hospital, third party, or government after bidding
- On-line bulk purchasing is the main manner for all drugs passed the economic and technical criteria, government encourages price competition between manufacturers

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## MC in pharmaceutical price setting (China) The issue and objective

- Before the new Drug Registration Regulation was enacted in 2007, SFDA granted 188,200 approval certifications for about 110,000 chemical medicines. The manufacturers only competed on price
- The generics stayed on imitation mode rather than prioritizing product quality and consistency
- China SFDA testing results showed a gap in quality between generic and originals drugs; the low quality of generic drugs has posed a threat to the safety of the public

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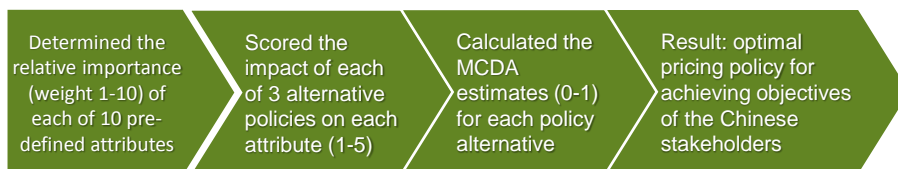
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## The political process - why a MC process?

- For Chinese generic products which have shown not to be significantly different from the originators in the quality consistency evaluation, the price gap to the originator products will be reduced
- The MC process allows for value based pricing
- In addition, NDRC will operate a reference pricing system which defines the reimbursement level; if the price is higher than the reference price, patients will pay the difference

## The MC process and the weighting

- Conceptualization:
  - In November 2013, an international group of health economist and health policy experts in the pharmaceutical field came together to develop a method of using MCDA for evaluating policies for off-patent originators and generic products
- Implementation in China:
  - Subsequently, 11 well-known academic experts and 7 pharmaceutical senior executives were interviewed in the MCDA survey in China



## MC in pharmaceutical price setting (China) Implementation of the MC process

### The Combined Scores of Each Attribute in Different Interview Group

	Attributes	Academia group	Pharma group
1	Pharmaceutical equivalence	0.11	0.11
2	Bio-equivalence	0.12	0.11
3	Pharmaceutical enterprise pass 2010 Chinese version of GMP	0.10	0.10
4	Clinical efficacy and effectiveness.	0.12	0.14
5	Drug safety	0.12	0.12
6	Patients adherence to therapy	0.10	0.09
7	Different excipients, production process and technology, shelf-life	0.11	0.11
8	Order of entry in the market	0.09	0.09
9	Supply reliability	0.08	0.08
10	Manufacturer Investment	0.06	0.05

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## MC in pharmaceutical price setting (China) Implementation of the MC process

### Total Scores in Different Pricing Policy Options

Groups	Policy 1 Pharmaceutical Equivalence	Policy 2 Value-based Pricing	Policy 3 Reference Pricing
Academia	0.72	0.70	0.62
Pharma	0.72	0.69	0.67

- The pharmaceutical equivalence consistency test for generics has been conducted by SFDA since 2012
- NDRC has proposed clinical value-based pricing in 2013, and will considered pilot study of reference (benchmark) pricing in 2014

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## MC in pharmaceutical price setting (China) Experiences

- The drug pricing system in China will be improved:
  - cost-based pricing plus price competition (supply and demand)
- Low price drug management will be based on market mechanism: the price will set by manufacturer, manufacturers compete on price, but the government controls the maximum retail price
- China will introduce an international reference price system to reduce the price gap between China and other countries (for innovative drugs)
- Using price incentives as a tool to promote innovation and drug quality
- Establishing objective multiple criteria indicators to establish a price accreditation system
- In the future,
  - government will control the drug price directly
  - third party\* control of medical expenditures and
  - market arbitrage of the price

\* Payers such as insurance companies

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2012-2014 Chair, ISPOR Asia Consortium Executive Committee

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## Decisions for the Essential Drug List (Thailand) The issue and objective

- National List of Essential Medicines (NLEMs): rationale drug use & reimbursement list
- ISaE score: I = information; S = safety; af = administration restriction score & frequency of drug administration score; E = efficacy
- ISaE score: good if closer to 1 & out if less than 50<sup>th</sup> percentile
- Objective: to assess benefits and risks of statins by MCDA (Wanishyakorn T, a PhD student)

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## Decisions for the Essential Drug List (Thailand) The political process - why a MC process?

- Primarily, policy makers (e.g. payers) and clinical experts are involved in the NLEM listing process.
- Key committee:
  - 20 therapeutic groups of experts
  - economic experts
  - Consolidating committee
- Why MCDA?
  - A tool that complements ISaE score
  - More involvements e.g. patient groups, practitioners

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## Decisions for the Essential Drug List (Thailand) The MC process and the weighting

- Identify benefits & risks
  - Literature review, Patients/experts/PTC interviews
  - Stroke, MI, Myalgia, Liver toxic
- Weighting
  - Swing weight in 6 patient grs/ 6 expert grs/ 10 policy maker grs
  - Discrete choice experiment (DCE): multinomial logit model
- Scoring/Ranking
- Sensitivity analysis

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## Decisions for the Essential Drug List (Thailand) Implementation of the MC process

	Weighting methods	Ranking					
		Atorva statin	Fluva statin	Lova statin	Prava statin	Rosuva statin	Simva statin
Patient (N = 24)	SW	1	3	2	5	6	4
Patient (N = 223)	DCE	1	4	3	5	6	2
Expert (N = 24)	SW	1	3	4	5	6	2
Expert (N = 63)	DCE	1	3	4	5	6	2
Policy maker (N = 40)	SW	1	3	4	5	6	2
Policy maker (N = 67)	DCE	1	3	4	5	6	2
Overall (N = 84)	SW	1	3	4	5	6	2
Overall (N = 353)	DCE	1	3	4	5	6	2

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## Decisions for the Essential Drug List (Thailand) Experiences

- An introduction of MCDA to health care decision making
- For MCDA, time is not an issue, but discretion, trust and power are
- Comfortable with existing tool e.g. ISafe, economic evaluation, BIA
- Need more examples, more criteria
- Patients know what they want. Let them share decisions.

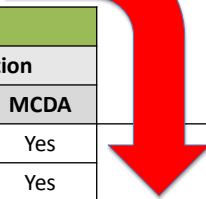
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## Decisions for the Essential Drug List (Thailand) Future for off-patent pharmaceuticals

		Approach			Perspective
		Registration	Selection		
			ISafe	MCDA	
Attribute	Efficacy	Yes	Yes	Yes	Patients
	Safety: SE, ADR	Yes	Yes	Yes	
	Safety: equivalence, excip & tech, GMP	Yes			
	Patient adherence		Yes		Providers
	QoL		(Yes)		
	Cost		Yes		Policy makers/ Payers
	Supply reliability				
	Added value e.g. pt edu				
	Stakeholder partnership				
Local investment					



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### Jie Shen

Head of Market Access, Emerging Markets  
Abbott, Basel, Switzerland

## Quality = Degree of Excellence

- Explained by
  - **Components contributing to Quality**
  - **Ways of measuring Quality**
  - **Methods used to improve Quality**
- Quality is NOT about the Standard of goods coming out of factory
- In the pharmaceutical industry, Quality needs to be built into the **entire process** from Product Development to Manufacturing and Post Marketing follow up

## Why Quality is important

- Purpose of healthcare interventions is to **improve the health status**
- **Any unpredicted event** such as adverse events or drug shortage due to defective products may harm patients and damage healthcare
- **Predictability in the drug development and manufacturing** is closely linked to a thorough and fact-based understanding and management of the entire manufacturing process including
  - Ingredient supply
  - Cost of goods sold
  - Inventory level
  - Ingredient quality
  - Technology development
  - Regulatory compliance
- **Quality assurance** delivers these integrated measures throughout the entire production process
- **Quality control** ensures that the output of the process reached the pre-defined specifications

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## Regulatory agency guidance on Quality

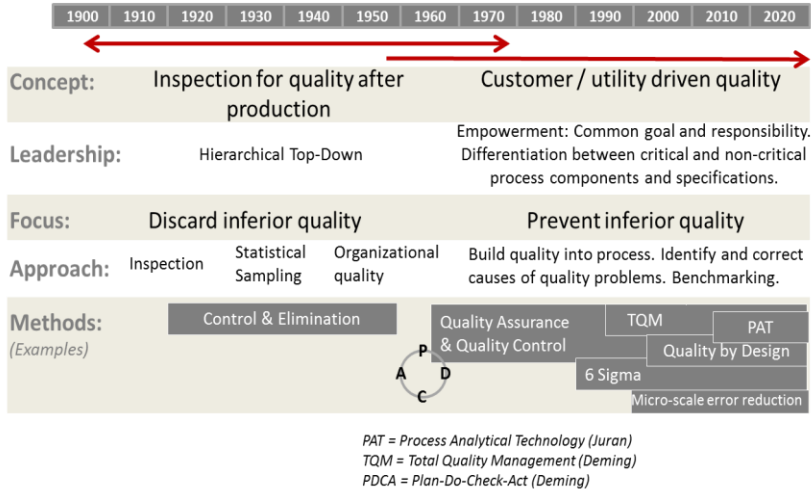
- Quality is built into pharmaceutical products (FDA, 2004) through a comprehensive understanding of
  - The intended therapeutic objectives; patient population; route of administration; and pharmacological, toxicological, and pharmacokinetic characteristics of a drug
  - The chemical, physical, and biopharmaceutical characteristics of a drug
  - Design of a product and selection of product components and packaging based on drug attributes listed above
  - The design of manufacturing processes using principles of engineering, material science, and quality assurance to ensure acceptable and reproducible product quality and performance throughout a product life cycle

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# Quality management method



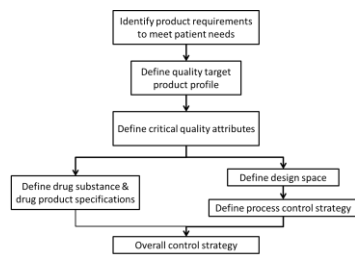
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# Quality by Design (QbD)

- QbD is a concept applied to the design, development and manufacturing of biopharmaceutical molecules that entails building quality into the process and product in a systematic, science- and risk-based manner (FDA 2006, 2007; ICH 2009)



Core elements and flow of developing QbD



QbD as an integrated approach with continuous adaptability

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## Process analytical technology (PAT)

- PAT is internationally defined as “a system for designing, analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality (EMA, FDA 2004, 2013)
- The goal of PAT is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. The types of tools used in a PAT framework are categorized as:
  - Multivariate data acquisition and analysis tools
  - Modern process analyzers or process analytical chemistry tools
  - Process and endpoint monitoring and control tools
  - Continuous improvement and knowledge management tools

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## Good Manufacturing Practices (GMP)

All existing guidelines have shared basic principles:

- **Clear definition and control of manufacturing processes.** Validation of all critical processes to ensure consistency and compliance with specifications.
- **Any changes** to the process are evaluated and validated if they have an impact on the quality of the drug.
- Instructions and procedures are written in clear and unambiguous language. (**Good Documentation Practices**)
- **Operators are trained** to carry out and document procedures.
- **Manual or electronic records** are made during manufacture to demonstrate that all the steps were taken which were required by the defined procedures and instructions and that the quantity and quality of the drug was as expected. Deviations are investigated and documented.
- **Records of manufacture (including distribution)** that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.
- The **distribution** of the drugs minimizes any risk to their quality.
- **A system for recalling** any batch of drug from sale or supply is available.
- **Complaints about marketed drugs** are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

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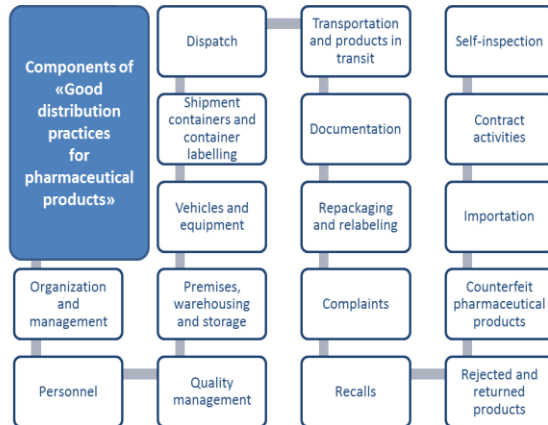
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## Good Distribution Practices

- Typical components of Good Distribution Practices (WHO example)



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## Cost and Value of Quality

«The bitterness of Poor Quality remains long after the sweetness of low price is forgotten»

--- Ben Franklin ---

### Investment is necessary

- Policy makers need to set quality expectations and control the performance of all suppliers
- Manufacturers need to invest in the processes, the training, the management systems, and the certification fees
- Payers and patients need to be prepared to pay higher acquisition costs for Quality

### Ignoring quality will incur costs

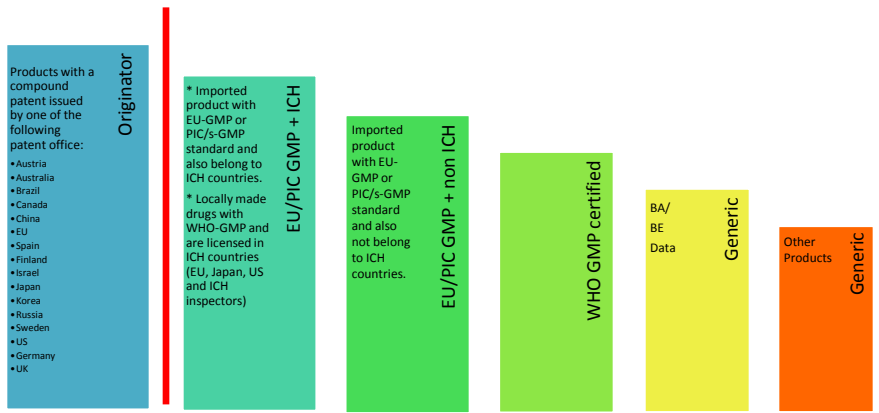
- Manufacturer will pay for producing scrap with material costs, wasted labor or litigation costs
- Healthcare systems will pay for the increased usage of healthcare due to low quality products and their negative impact
- Patients will pay with their personal health

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## Example: The use of quality to categorize off-patent pharmaceutical products in Vietnam



PIC: The Pharmaceutical Inspection Convention

ICH: The International Conference on Harmonisation. ICH thus represents 17 countries comprising 15% of the world's population and accounting for 90% of the US\$ 320 billion global pharmaceutical sales of the year 2000

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## Using weighted criteria for making reimbursement decisions for off-patent pharmaceuticals in China, Thailand and Vietnam

- Introduction of Faculty, Agenda D. Brixner
- Use of weighted criteria for decision making for generics D. Brixner
- Implementation of multi-criteria decision process for tender decisions in Beijing (China) SL Hu
- Analysis of using MC in pharmaceutical price setting (China) SL Hu
- Decisions for the Essential Drug List (Thailand) S Ngorsuraches
- Quality of pharmaceutical products and the classification of products for tender in Vietnam J. Shen
- Discussion D. Brixner

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Do any of you (audience or on panel) have examples of how some, or any one of the criteria mentioned have been used in generic purchasing decisions?

1. Proof of pharmaceutical equivalence
2. Proof of bio-equivalence
3. Differences in formulations, excipients and process technology
4. Effect on patient adherence
5. GMP (*Good Manufacturing Practice*) and Quality standard
6. Supply reliability
7. Added value (*e.g. patient educational services, outcomes solutions*)
8. Stakeholder partnership (*e.g. Public-private-partnership*)
9. Local investment (*e.g. manufacturing, R&D, employment*)
10. *Other according to local policy priorities (work conditions & benefits, environmental standards etc.)*

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What are risks associated with only considering cost in purchasing generics? Do any of you, in audience or panel, have any examples of risk?

Quality issues

Lack of bioavailability

Safety issues - Adverse events

Lower adherence

Too frequent switching

Drug shortages

Reduced willingness to invest

Disadvantage of local industry

OTHERS?

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## Who should sit on the table when making pricing, coverage or purchasing decisions?



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## How can success of off-patent policies be measured?

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