

# Sustaining Efficiency and Regulatory Compliance in a Global Quality Control Laboratory Network

Implementation of Best Practice in Operations and Quality Systems

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WHEN YOU NEED TO BE SURE



- The challenges of growth in an international company
- Implementation of best practice
  - Six sigma
  - KPI measurement
  - Implementation of common IT systems
  - Sharing resources
- Ensuring regulatory compliance
  - Choosing the right quality system(s)
  - Global QA system
  - Global vs. local SOPs
  - Cross-auditing

# HOW TO COPE WITH THE GROW OF A COMPANY?

- Increase of efficiency
  - Use of assets
  - Use of human resources

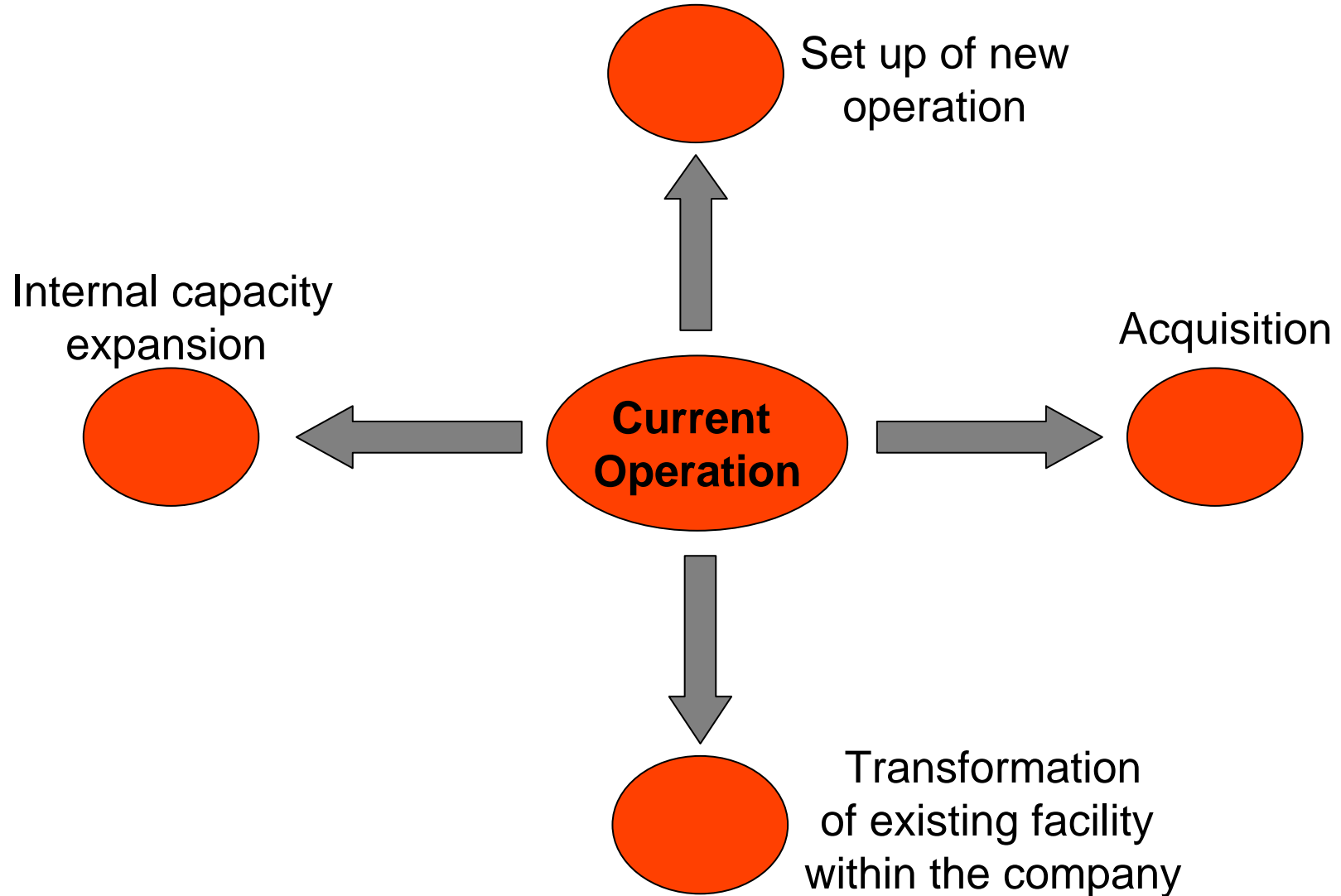
=> making more with the same amount of resources

- Investments in capacity
  - People (manpower)
  - Assets

=> making more with more resources



## EXPANSION OF CAPACITY



## EXAMPLES OF RECENT ACQUISITIONS BY INDIAN PHARMA COMPANIES

<b>Buyer</b>	<b>Target</b>	<b>Price</b>	<b>Country</b>
Dr. Reddy's	Betapharm	570m US\$	Germany
Ranbaxy	Terapia	324m US\$	Romania
Ranbaxy	GSK Generics	undisclosed	Italy
Nicholas Piramal	Pfizer manufacturing plant	undisclosed	UK
Orchid	Bexel Pharma		US
Strides Arcolab	DHA	13m US\$	Singapore
Zydus Cadila	Liva Healthcare	undisclosed	India
Actavis	Lotus Labs	25m US\$	India
Mylan	Matrix	736m US\$	India
<i>Mylan</i>	<i>Merck Generics</i>	<i>4.9bn €</i>	<i>Germany</i>

## THE CHALLENGES OF GROWTH FOR SGS

- Establishment of Life Science Services Business Unit 2002
- Two business areas:
  - Clinical Research Organization
    - Focus on early stage clinical services
      - Phase I
      - Bioanalysis
  - Quality Control Testing
    - Build a global network of QC labs
    - Expand into QC testing of biopharmaceuticals
    - Create expertise & experience in advanced (modern) testing services

## GROWTH OF A GLOBAL QC LABORATORY NETWORK

- Started with 3 dedicated QC laboratories
  - Canada
  - France
  - Belgium
- Additionally, 1 Pathology laboratory
  - Peru
- 2 Drug Abuse testing laboratories
  - Taiwan
- CAGR of 12% to >30% in 03-06
  - Significant expansion of internal capacity

## TRANSFORMATION OF EXISTING FACILITIES

- Separation of pharmaceutical QC activities out of a multilab facility in Fairfield, US
  - Focused on testing of consumer goods in the past
    - Chemicals, cosmetics, plastics, raw materials
  - Transformed laboratory into dedicated cGMP compliant QC laboratories
- Similar approach in Bangkok, Thailand, and Hong Kong
  - Dedicated laboratories within lab complex
- Gradually adding QC testing capabilities to the Drug Abuse testing labs in Taiwan

## SET UP OF NEW OPERATIONS

- Separation of pharmaceutical QC services and move into dedicated new laboratory in Chennai, India
  - Purpose-built facility for analytical chemistry, microbiology, stability testing, biotechnology and toxicology studies
- Start up laboratories in Singapore and Shanghai, China
  - Stand alone operations within “SGS building”



- Acquisition of Institut Fresenius, a leading German testing lab network
  - Tradition of more than 150 years in business
  - Adding two QC testing labs
    - Berlin, stand alone laboratory
    - Taunusstein, laboratory within “SGS building”
  
- Acquisition of Northview Laboratories, USA
  - Family owned laboratory network
  - Adding two dedicated QC laboratories
    - Northbrook, IL
    - Spartanburg, SC

## GROWTH OF A LAB NETWORK

### Americas

#### Canada

★ Mississauga, Ontario

#### USA

★ Fairfield, NJ  
★ Northbrook, IL

### Europe

#### Belgium

★ Wavre

#### France

★ Clichy (Paris)

#### Germany

★ Berlin  
★ Taunusstein

### Asia

#### Taiwan

★ Taipéh  
★ Kaohsiung

#### China

★ Shanghai  
★ Hong Kong

#### India

★ Chennai

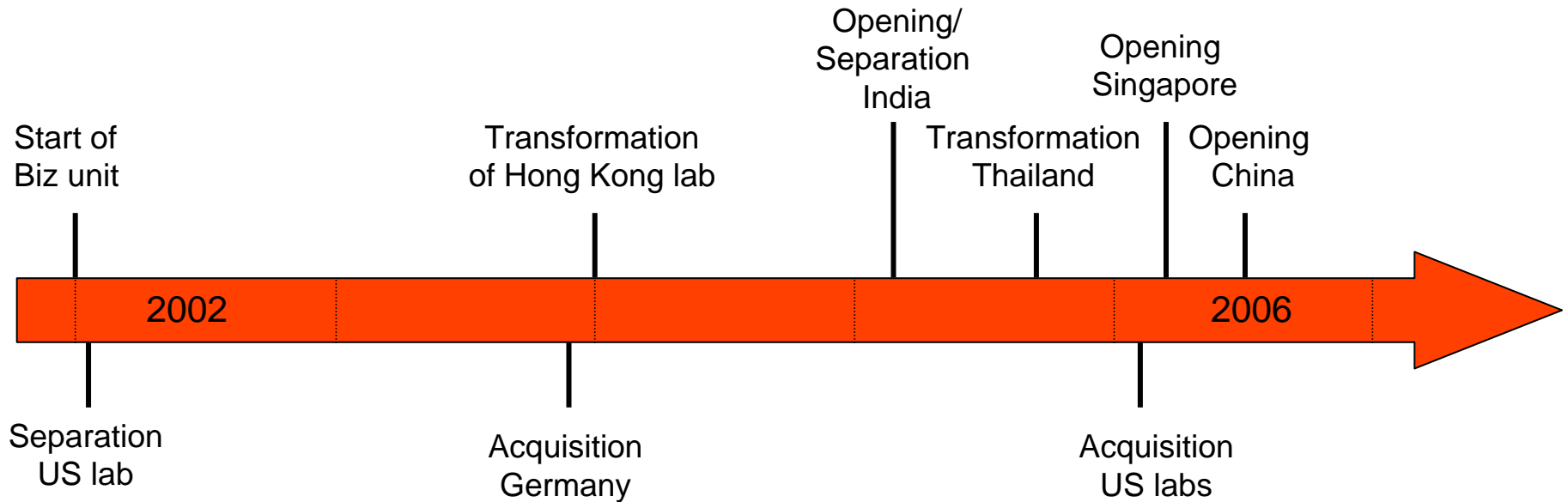
#### Thailand

★ Bangkok

#### Singapore

★ Singapore

## CHRONOLOGICAL ORDER



- Today a global network of 14 laboratories in 11 countries
- Dedicated to analytical services to the pharma, biopharma and medical device industry

## THE CHALLENGES ALONG THE ROAD

- Different organizational / reporting structure
- Different QA systems
  - Different SOP's
  - GMP, GLP and/or ISO (9001 and 17025)
- Different processes
- Different IT systems
  - LIMS
  - CRM
  - Accounting
- Different equipment
- Different languages and terminology
- Cultural differences



# Implementation of operational best practice

# APPLYING SIX SIGMA-LIKE TOOLS IN THE QC LABORATORY

## ■ DMAIC or DMADV approach?

### ■ DMAIC

- **Define** the project goals and customer (internal and external) deliverables
- **Measure** the process to determine current performance
- **Analyze** and determine the root cause(s) of the defects
- **Improve** the process by eliminating defects
- **Control** future process performance

### ■ DMADV

- **Define** the project goals and customer (internal and external) deliverables
- **Measure** and determine customer needs and specifications
- **Analyze** the process options to meet the customer needs
- **Design** (detailed) the process to meet the customer needs
- **Verify** the design performance and ability to meet customer needs

## APPLYING SIX SIGMA-LIKE TOOLS IN THE QC LABORATORY

- “The DMAIC methodology should be used when a product or process is in existence at your company but is not meeting customer specification or is not performing adequately.”
- “The DMADV methodology should be used when:
  - A product or process is not in existence at your company and one needs to be developed”
  - The existing product or process exists and has been optimized (using either DMAIC or not) and still doesn't meet the level of customer specification or six sigma level”
- Given the various different systems SGS has chosen the DMADV approach

## DEFINE THE PROJECT GOALS AND CUSTOMER (INTERNAL AND EXTERNAL) DELIVERABLES

- The aim of this project was to analyze the QC labs regarding:
  - Their portfolio
  - Their efficiency
  - Their cost structure and prices

# MEASURE AND DETERMINE CUSTOMER NEEDS AND SPECIFICATIONS

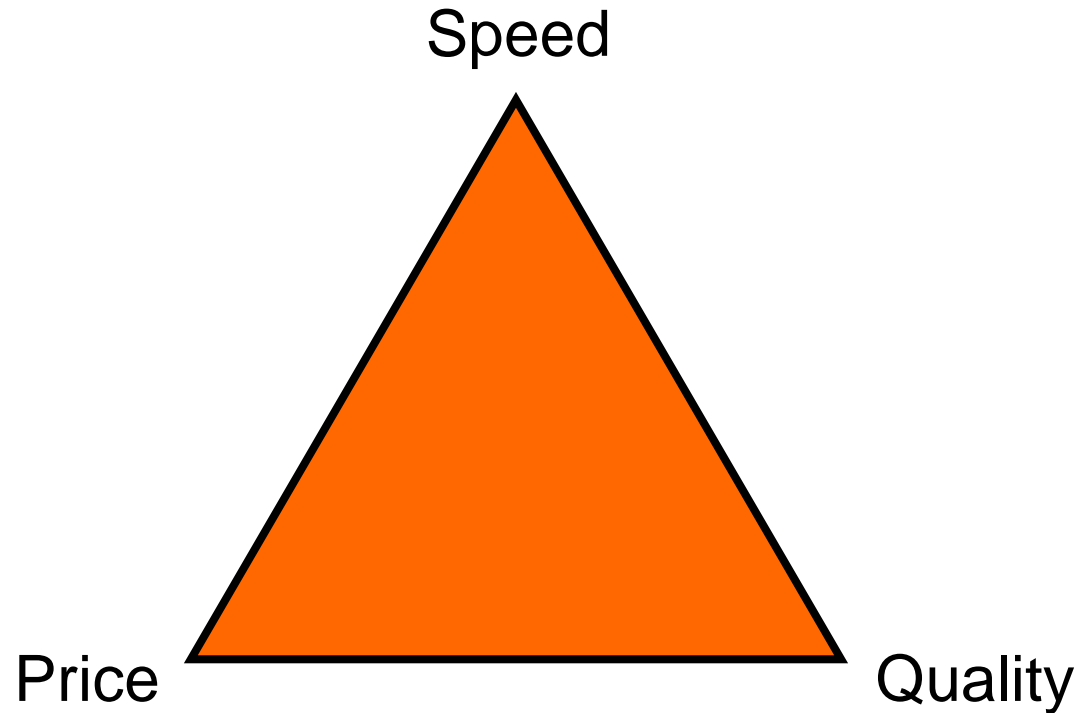
- External and internal customers
  - Surveys
  - Questionnaires
    - Face-to-face
    - Phone
    - Electronic
    - Statistically significant
  
- Phone or face-to-face meetings with representative clients of all labs
  - >50 customers contacted

Issues in communication	Average	Min	Max	Median
Experienced person	9,1	7	10	9
Reactivity	9,0	6	10	9
Easy reachable person of contact	8,7	6	10	9
Pro-active communication	8,5	2	10	9
Single person of contact during project	8,1	2	10	8
Ability to give technical advice	8,0	2	10	8
Possibility to have face to face meeting	7,4	2	10	8
Type of language	6,6	1	10	7

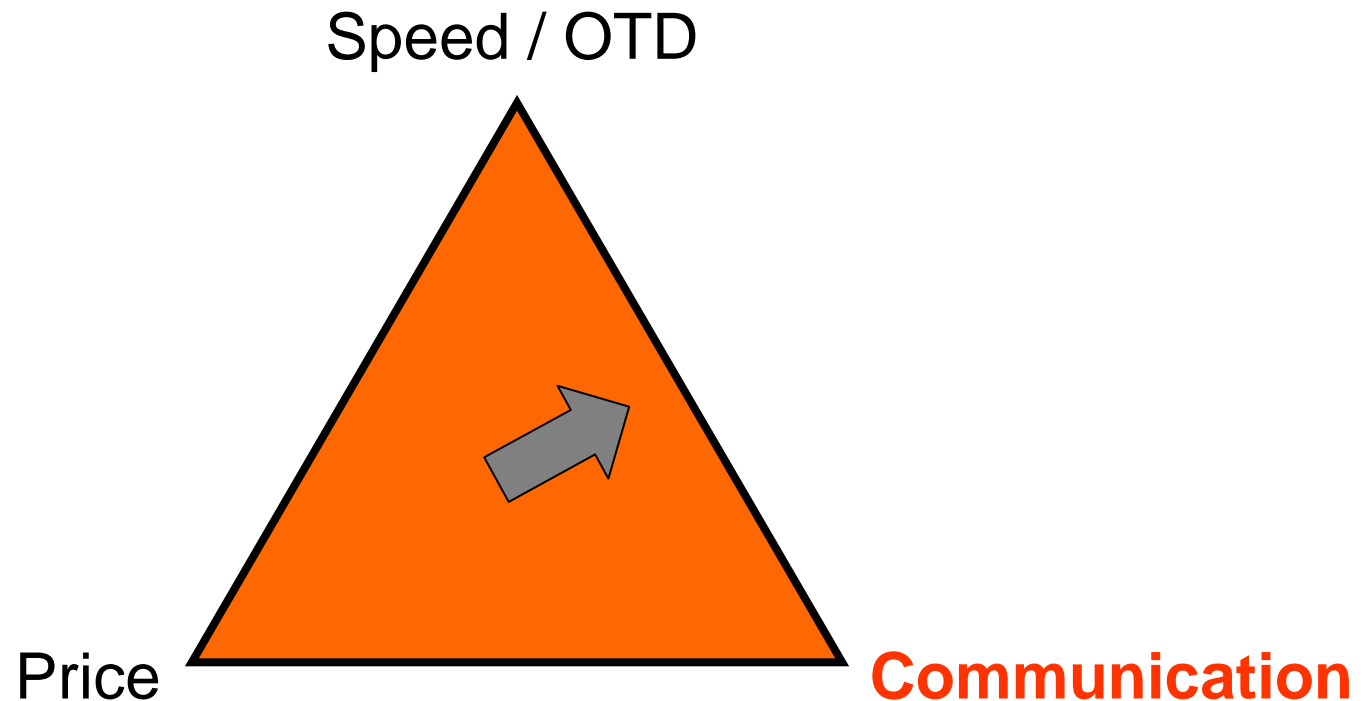
Issues about quality	Average	Min	Max	Median
Lab with pharmaceutical recognition by the official authorities of your country	<b>9,3</b>	5	10	10
FDA inspected	<b>7,6</b>	2	10	8,5
Being audited by other big companies (and accepted)	<b>6,0</b>	1	10	7
ISO certificate	<b>5,3</b>	1	10	5

Other issues	Average	Min	Max	Median
Flexibility in case of urgent needs	<b>9,2</b>	8	10	9
Respect of agreed timelines	<b>9,2</b>	7	10	10
Experience in the field	<b>9,0</b>	6	10	9
Ability to work following customer's SOP	<b>8,0</b>	2	10	9
Cost	<b>7,9</b>	5	10	8
Previous Collaboration	<b>7,6</b>	5	10	8
High turnover of equipment/qualification level	<b>7,5</b>	5	9	8
Low turnover of staff	<b>7,4</b>	5	10	7
Proximity	<b>7,0</b>	2	10	7
Large capacity in terms of staff	<b>6,9</b>	3	10	7
Large organisation / International recognized company	<b>5,9</b>	2	9	6,5

**OLD PARADIGM:** THE CUSTOMER CHOOSES THE BEST OPTION BETWEEN SPEED, QUALITY AND PRICE



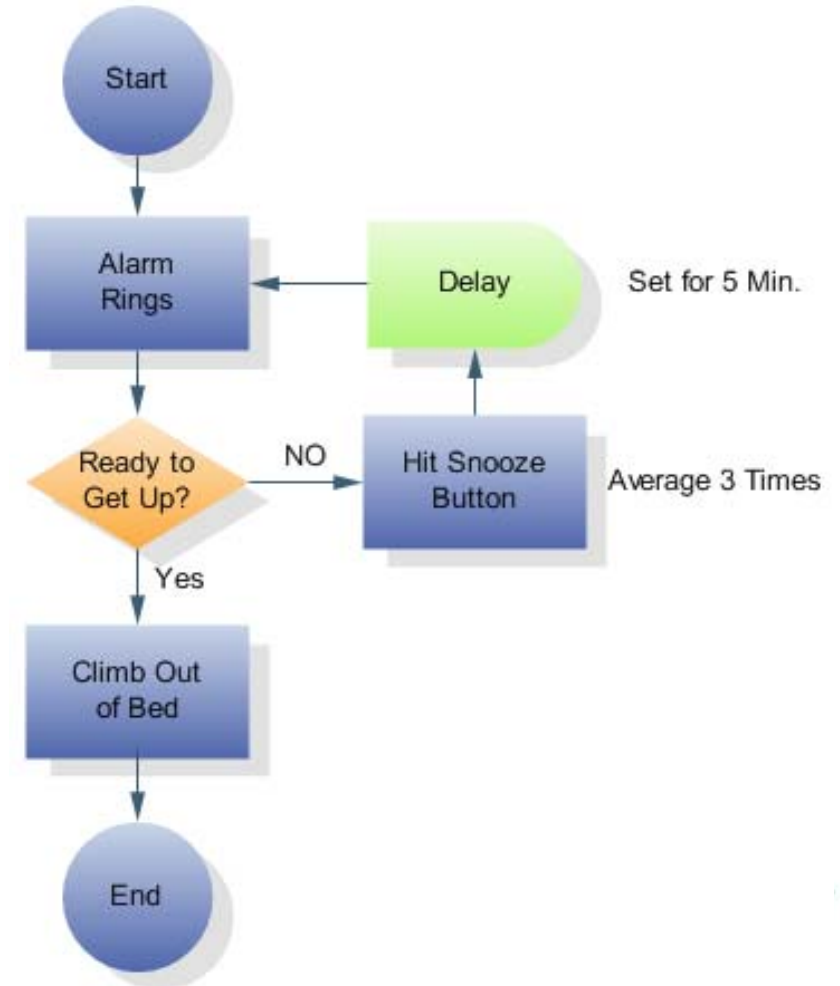
**NEW PARADIGM:** THE CUSTOMER CHOOSES THE BEST OPTION BETWEEN SPEED, PRICE AND COMMUNICATION



Quality is a must and not negotiable (almost)

# ANALYZE THE PROCESS OPTIONS TO MEET THE CUSTOMER NEEDS

- Map the processes
  - Breaking down processes into individual process steps
- Map responsibilities
  - Who's doing what?



# ANALYZE - LACK OF FOCUS

number of FTE
managing of entire operation
answering customer calls
calculation of quotes; generation of proposals and project plans
Sending of proposals to customer
Managing/ Monitoring of projects
entering samples into (LIMS) system
compilation of necessary information for lab
scheduling work, assign projects to analysts
training of analysts in technical aspects
performing analyses
documentation of analyses (log book/ LIMS)
calibration and qualification of instruments
Troubleshooting (analysis method, equipment)
OOS handling
Review of data (2nd / 3rd party review)
documentation/ compilation of reports
signing of CoFA
sending of CoFA/ reports/ raw data to customer
Management of Quality System
execution of GMP training
realization of internal/ external audits
sending of invoice to customer
ordering of equipment, columns and reagents
admin work, typing, fax, mail
cleaning of glassware/ labware
other
Number of tasks performed
number of tasks

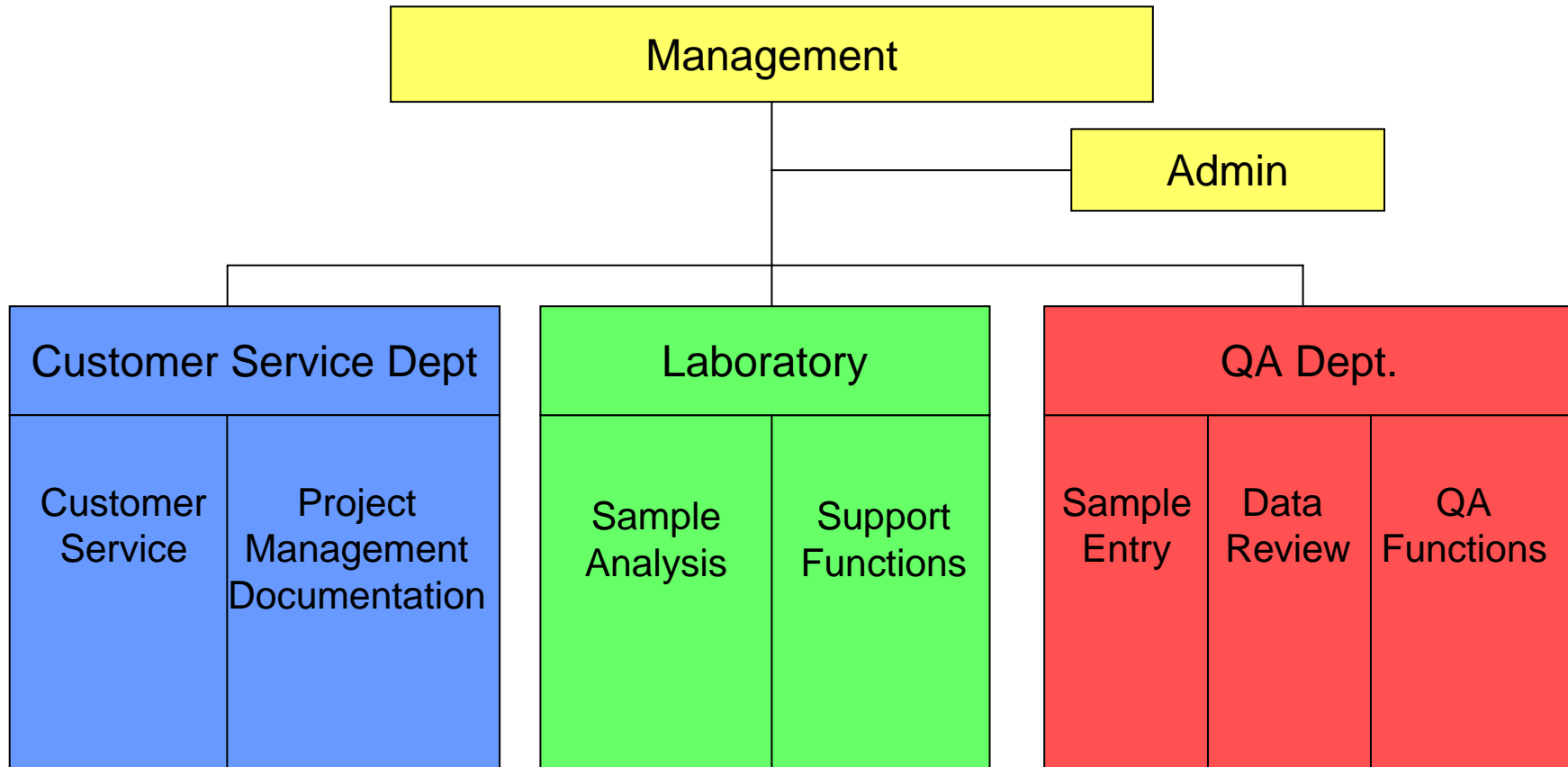
lab managers	1	10.0	5.0	12.0	1.0	5.0	2.0	14.0	10.0	5.0	2.0	10.0	10.0	1.0	1.0	2.0	5.0	5.0	17	8		
lab supervisors/team leaders/deputy manager	4	5.0	6.8		2.8	3.5	3.3		1.3	3.0	5.3	60.3	2.5	2.0	1.0	0.5	3.0		14	6		
lab coordinators (senior analysts)	9	0.3	1.6		1.7	2.3	4.0	69.8	6.6	4.2	0.8	3.0	1.9			3.6	0.3		13	3		
analysts	25				4.6	0.4	2.0	69.8	16.8	0.4	0.0	0.0	1.9			0.2	0.2	3.6	8	2		
cleaning	3														3.3			73.3	23.3	3	2	
project managers	2	10.0	5.0	25.0	5.0	5.0				5.0	22.0		1.0	5.0	5.0	2.0		10.0	12	7		
documentation																						
sample entry	2	1.3	3.8	0.6		37.5	1.3		10.0				2.3	1.6	0.9	0.9	7.1	19.8	13.1	13	4	
assistant project manager	0.68													35.0	1.0	4.0	2.0	50.0	8.0	6	2	
customer service	1.2	40.0	50.0	10.0																3	2	
administration	0.9	5.0				5.0						5.0	5.0			5.0		65.0	10.0	7	3	
quality	5.3	0.9	0.2	0.8	1.8	0.2	5.8	1.1	2.6	32.1	7.7	5.8	0.9	2.0	17.0	0.8	15.5	4.0	0.8	18	6	
management	3	16.3	20.0	1.7	3.3	10.0	6.7		1.7	1.7	5.0	6.7		5.0	7.7	1.7	4.3	8.3		15	8	
responsible reagents, standards, ...	1.5		4.0		5.0		3.0								5.0			63.0	5.0	15.0	7	3



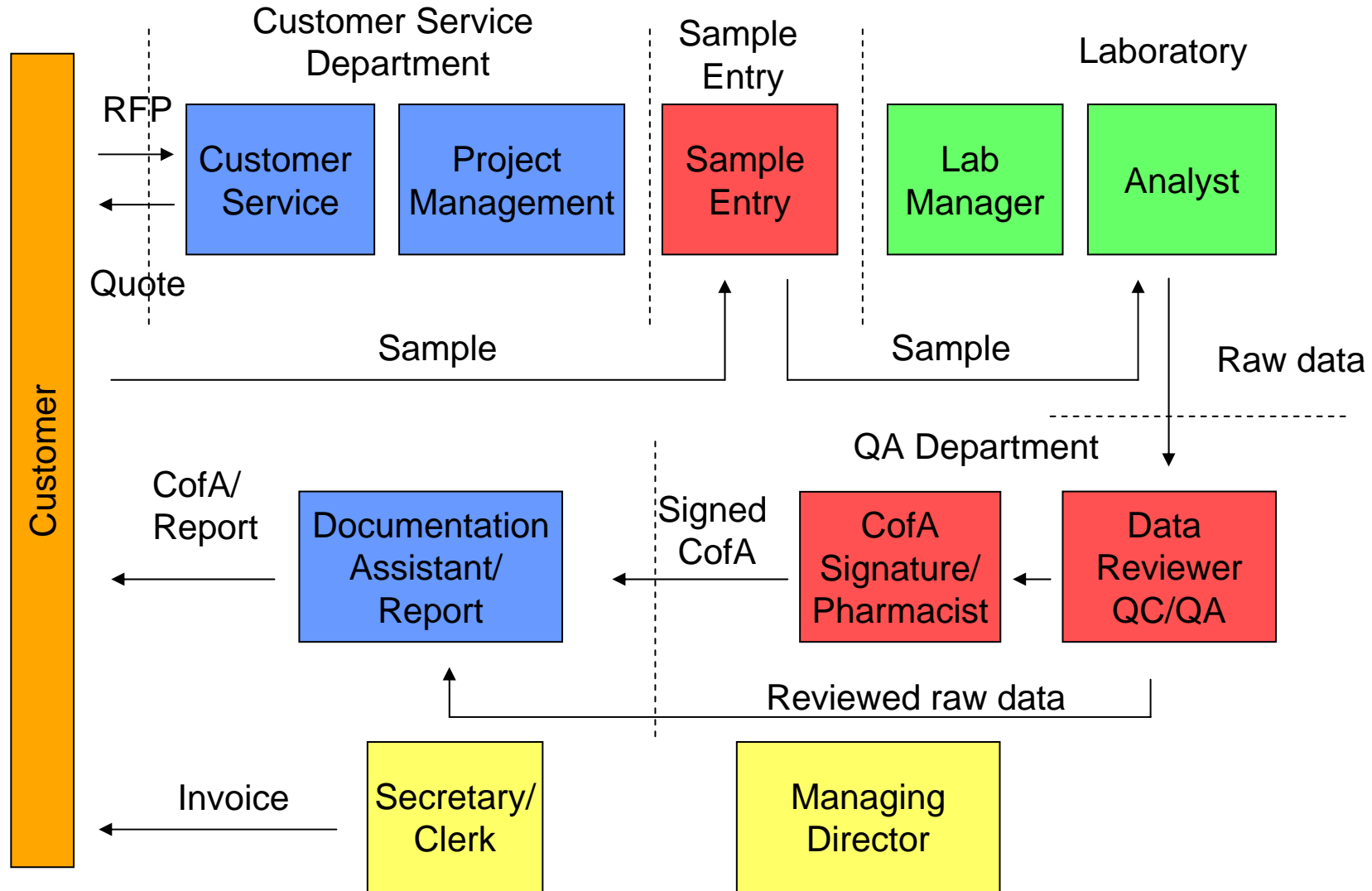
## DESIGN (DETAILED) THE PROCESS TO MEET THE CUSTOMER NEEDS

- Respect on-time-delivery of results (OTD)
- Streamlined customer communication
- Flexibility / Reactivity in case of urgent need
- Experience in the field / experienced person
- Full regulatory compliance
  - Independence of QA functions

# DESIGN - HARMONIZED STRUCTURE



## DESIGN - HARMONIZED PROCESSES



## DESIGN CREATION OF “CENTERS OF EXCELLENCE”

- Provide “standard” service portfolio at all laboratories
- Set up global and/or regional centers of excellence
  - Ensures experience and expertise with technology & methods
    - Retention of staff
    - Faster learning curve
  - Limits capital expenses for assets
    - Facilities & equipment
- Analytical areas
  - Stability studies
  - Analysis of biologics / viral testing
  - Analysis of cytotoxic/cytostatic substances
  - Extractables / leachables studies

# VERIFY THE DESIGN PERFORMANCE AND ABILITY TO MEET CUSTOMER NEEDS

- KPI measurement
  - Internal
  - Monthly
  
- Customer satisfaction survey
  - External
  - Annually

- Focus on **KEY** performance indicators
  - Don't try to measure everything
- KPI should be objective
- Use electronic / IT tools to measure KPI
- Set limits/ranges for KPI
- Variance from limit/range should trigger action
  
- Measuring KPI raises awareness and drives improvement by itself
  - Self-control
  - Internal competition

- Customer needs related
  - On-time-delivery of results [%]
    - From sample receipt to delivery of report
    - Including measurement of S.D.
  - Turn-around-time [days, hours]
    - By department
    - Break down into process steps
      - » Sample receipt to analysis
      - » Analysis time / raw data
      - » Release of raw data
      - » Release of CofA / report
  - Reactivity, TAT for RFI
- Financial metrics
- Operational performance
- Quality and compliance



- LIMS (Laboratory Information Management System)
  - A common LIMS systems drives harmonization by itself
    - But harmonize first before installing the LIMS
  - Allows automatic KPI reporting
  - Supports the “center of excellence” approach
    - Full traceability of sample status
  - Automatic customer notification
    - Sample receipt
    - OOS
    - Certificate of Analysis
- CRM (Customer Relation Management System)
  - Ensures proper customer communication
- Accounting systems

- Increased purchase power
  - Equipment purchase for more than 500 laboratories
  - Service agreements
- Easy and reliable installation
  - Standard protocols for IQ, OQ, PQ
- Rapid method transfer
- Training of employees
- Calibration services
  - Common internal service group
  - Shared service equipment
    - E.g. Data loggers
- Service and maintenance
  - Common schedules

# Sustaining Regulatory Compliance

WHEN YOU NEED TO BE SURE



# SETTING UP A COMPLIANT LABORATORY QA SYSTEM

- GMP, GLP, or ISO
- Documentation
  - Notebooks or controlled lab sheets
  - Electronic or paper
- Equipment qualification
- Method validation
- OOS
- CAPA
- Deviation
- Change control
- Training



## CHOOSING THE RIGHT QUALITY SYSTEM(S)

- GMP (cGMP, EU-GMP) is the standard in US and Western European pharma industry
  - US and European GMP varies slightly
  - Some German “Regierungsbezirke” (local regulatory authorities) don’t issue GMP certificates for contract labs
  - Similar situation in Singapore
  - France and Belgium require a pharmacist to sign CofA
- India requires GMP compliance
  - Guidelines close to WHO-GMP

- Chinese and Hong Kong authorities have certification based on ISO 17025
  - Until recently contract testing for batch release was not allowed under Chinese GMP
    - Law changed June 2007
    - Unclear about lab accreditation
  - GMP standards will be raised
- Thailand and Taiwan do not require GMP; accreditation scheme based on ISO 17025

# GMP IS NOT STATIC

## RECENT CHANGES IN GMP GUIDELINES

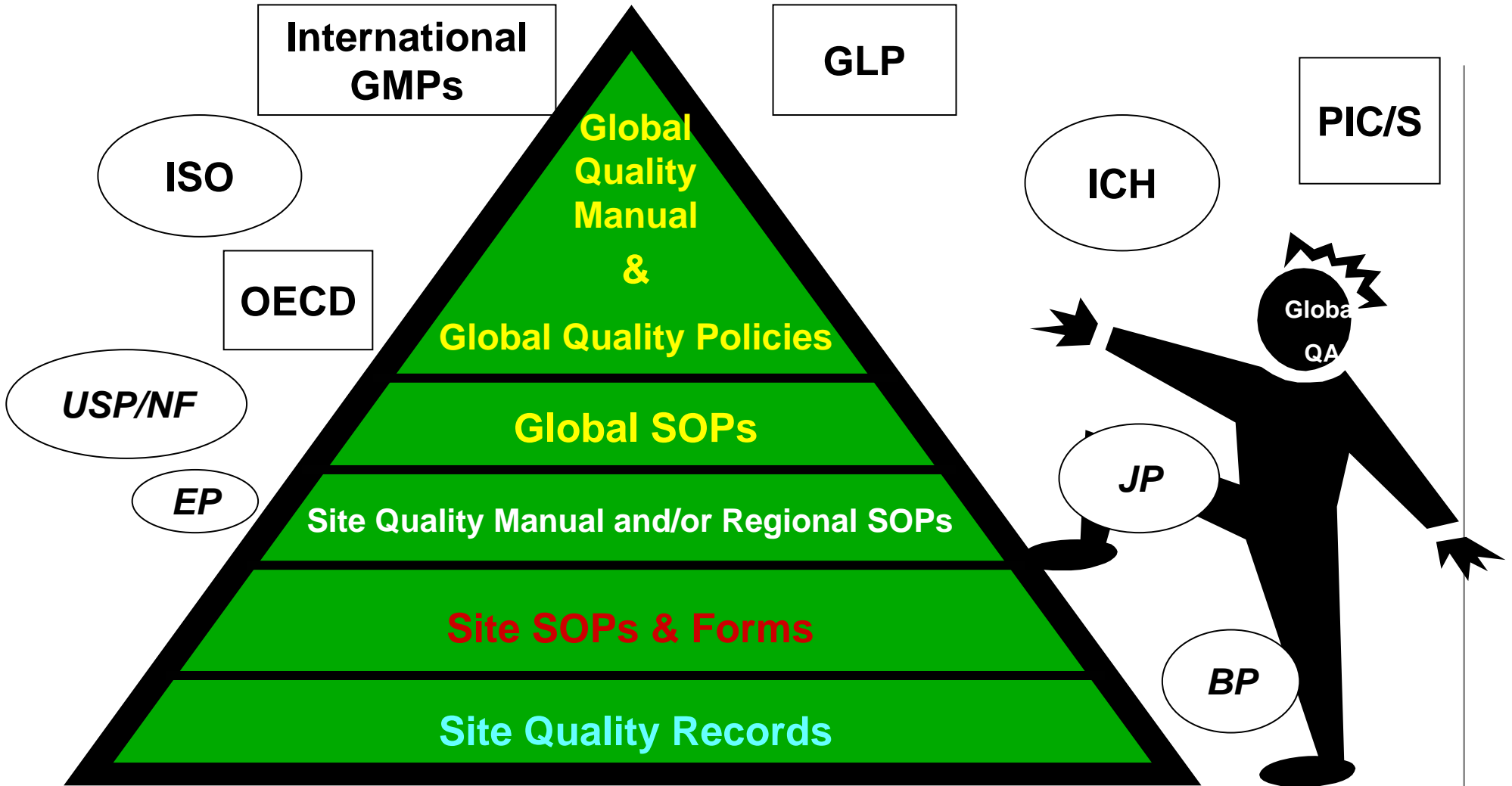
- Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach
  - US FDA, September 2004
- 21 CFR Part 11, Electronic Records; Electronic Signatures
  - US FDA, March 2000
- EU Directives 2001/83/EC and 2001/82/EC, GMP compliance of API manufacturers
  - EMEA, October 2005
- Introduction of GMP in China
  - SFDA, Dec 1999 – June 2004
  - Revised law issued 2007
- Drug and Cosmetics Act, Schedule M
  - CDSCO India, last update Oct 2005

## GMP FOR INTERNATIONAL ISO FOR LOCAL LABORATORIES

- Full GMP compliance for all laboratories serving international clients and/or clients serving international markets
  - US, Canada, France, Belgium, Germany
    - Some have GMP, GLP and ISO
  - Singapore
  - India
    - Passed US FDA audit in Feb 2007
    - GLP compliant and ISO certified
  - China
    - ISO 17025 certified, CNAL
    - Gradually upgrading to GMP
  
- ISO 17025 for laboratories serving local markets
  - Thailand, Taiwan, Hong Kong

## IMPLEMENTING A GLOBAL QA SYSTEM

- Global Organizational Change by adding functional support at the global level:
  - Global Quality Assurance (GMP & GLP)
  - Global Business management structures (QC)

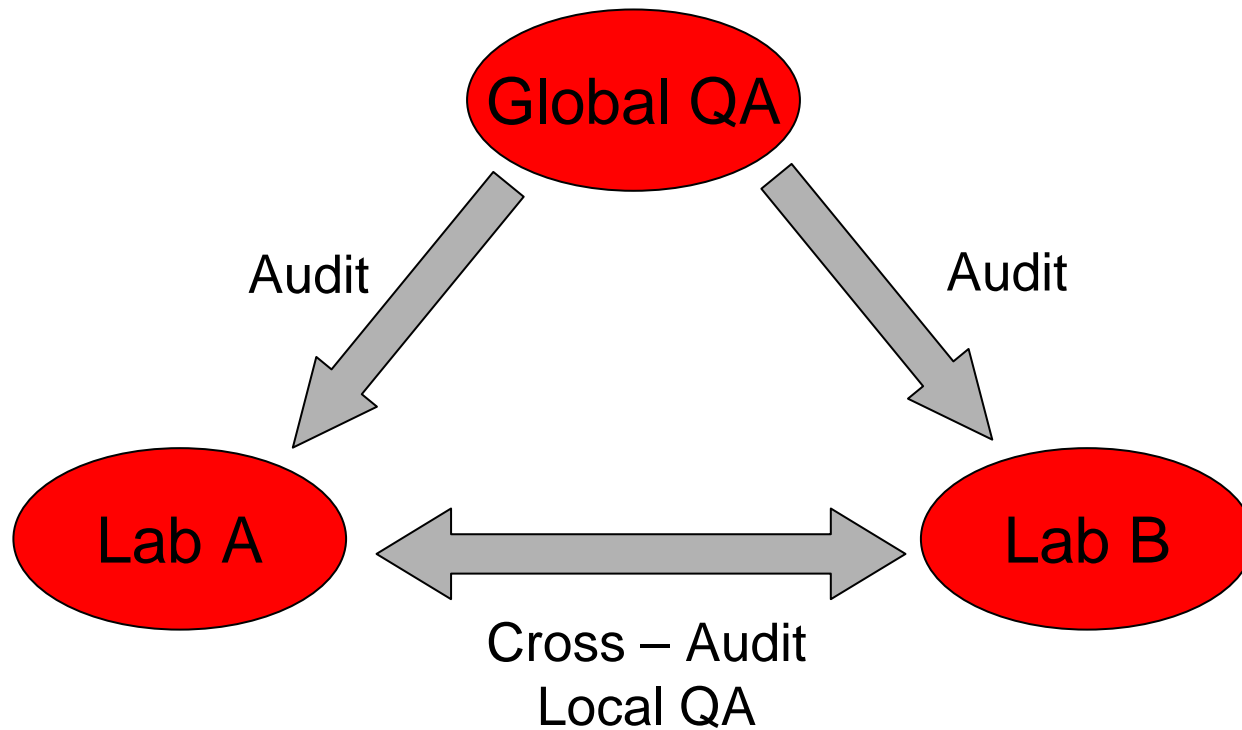


# GLOBAL KPI'S FOR QUALITY AND COMPLIANCE

- KPIs are custom-designed for Contract Testing Labs
- Customer Service and Finance
- Lab Operations
  - OOS
  - Obvious lab errors (OLE)
  - Repeat tests
  - Unplanned deviations
  - Utilization rate of equipment
- Quality and Compliance
  - Inspections and observations
  - Complaints
  - Corrective and preventive actions (CAPA)

## OTHER QUALITY & COMPLIANCE ACTIVITIES

- Global QA Audits of all Sites and including cross-auditing
- Global QA communication e.g. site observations, regulatory trends, etc.
- Global QA website e.g. Global quality documents, Questions and Answers Blog, Regulatory links
- Global QA Training to all Sites
- Special GxP training to new sites



## CROSS AUDITING BENEFITS

- Awareness of areas of shortcomings
  - Proactive correction and prevention
  - Reduces non-compliance in future audits
- Active participation in system improvements
- Joint solution on interpretation of regulatory guidelines
- Sharing experience of regulatory and client audits
- Alert system for local regulatory changes
- Replacing client audits
  - Clients audit one lab and rely on cross-audit reports of other labs with same QA system
- Audit of QA groups

- Modern management tools ensure improved efficiency
  - 6 sigma
  - Benchmarking
  - KPI measurement
- Common structures allow for cost savings
  - Equipment
  - Maintenance
  - Transfer of projects
- Global QA systems ensure compliance with regulatory guidelines
  - Rapid adaptation to changing guidelines
  - Savings in hosting client audits