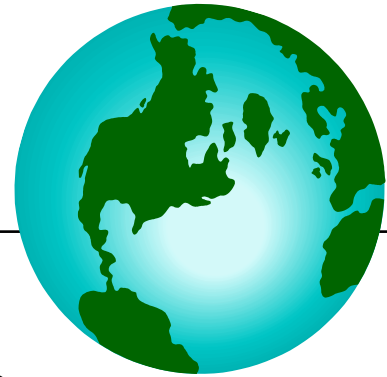

Lilly Perspective on East Asian Development – Past, Present & Future

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Global Regulatory Affairs
Eli Lilly and Company

Lilly

Answers That Matter.

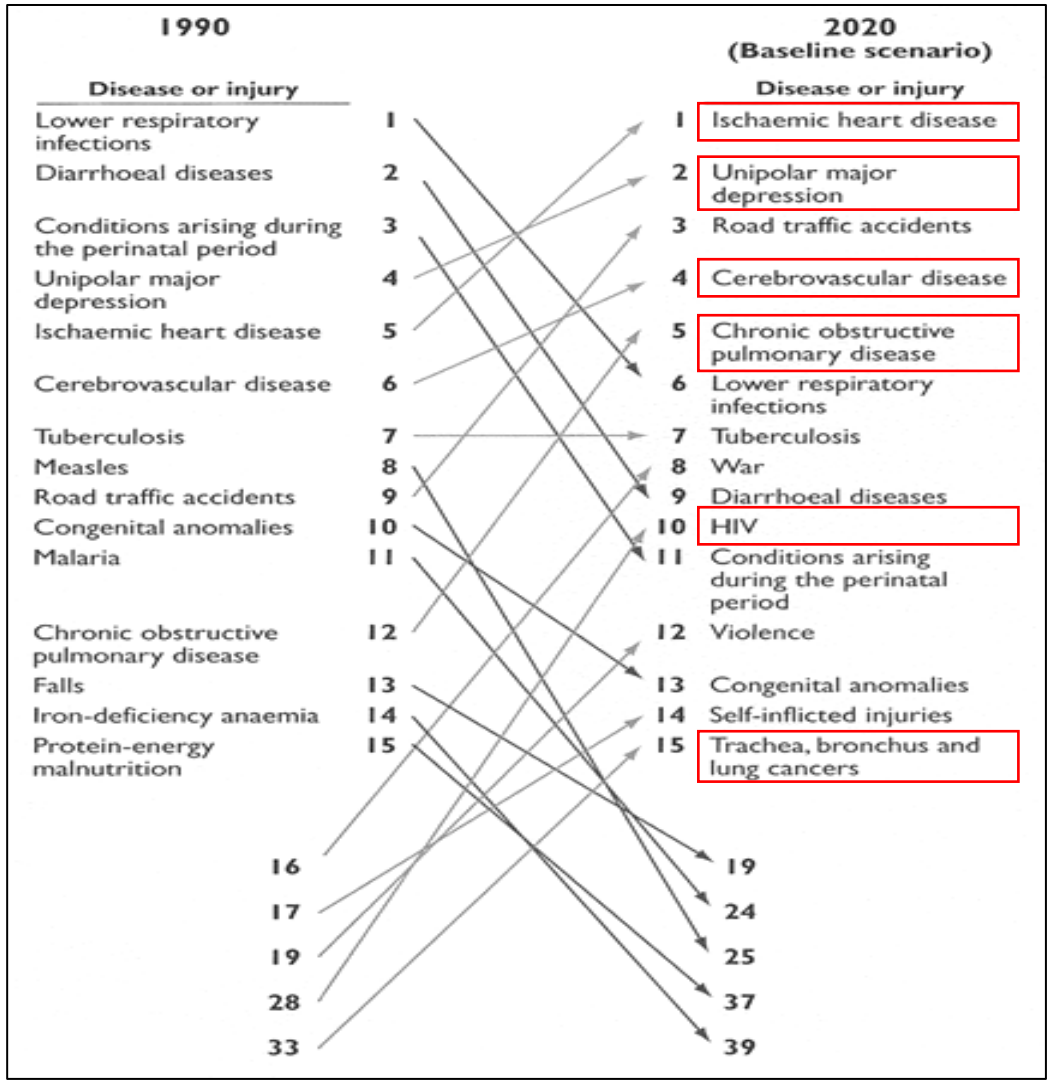
Agenda

- Background
- Past experience
- Present activity
  - Improvements
  - Successes
- Future
  - Strategy
  - Challenges
  - Opportunities

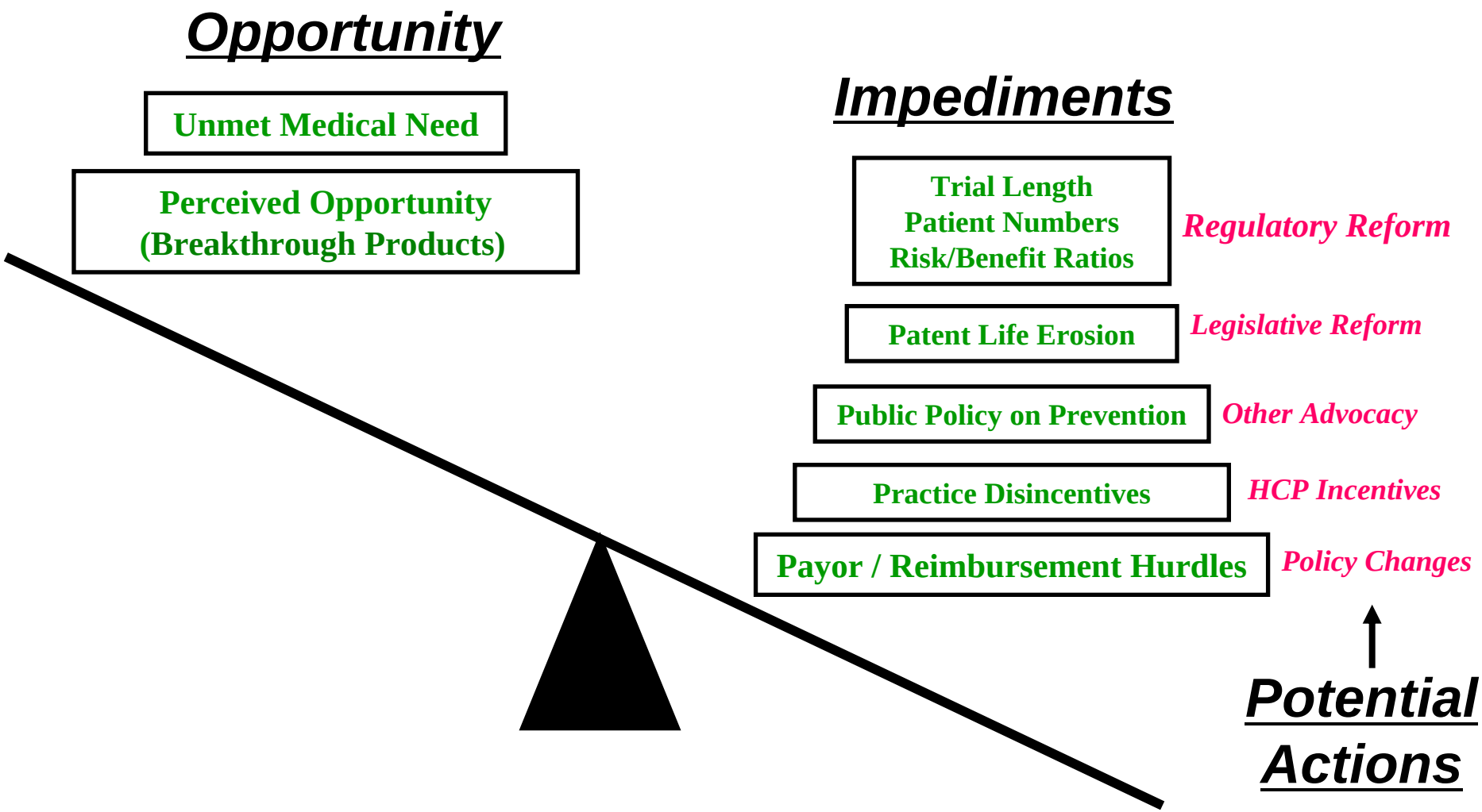
Development Landscape: Opportunities/Needs

Change in the rank order of disease burden for 15 leading causes, world 1990-2020

--WHO 2020

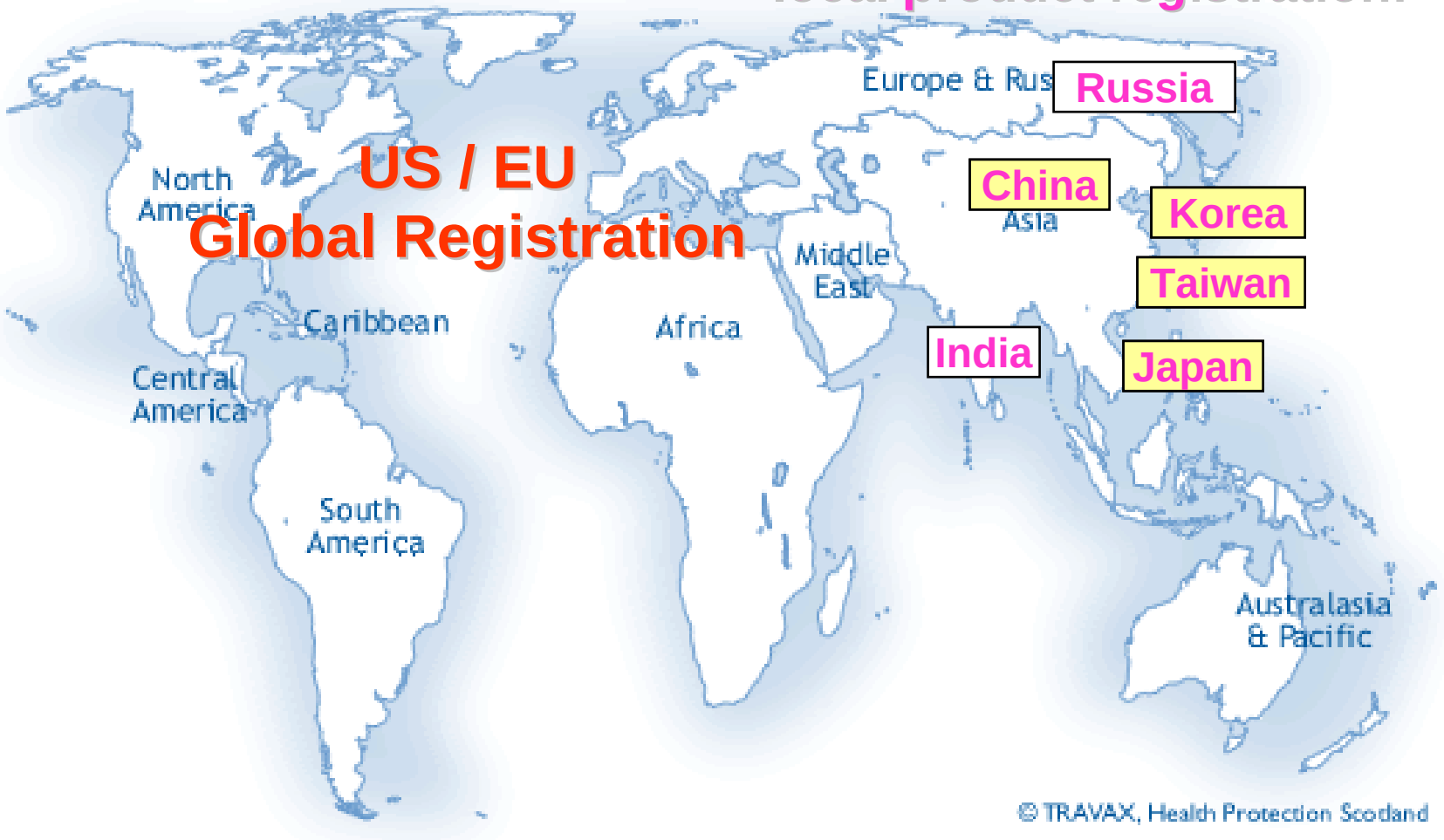


Background: Opportunities & Impediments



East Asian Registration

Local data required to support local product registration:



East Asia Past…*since ICH*

Individual region development strategy

Little or no collaboration between regulators

No cross regional guidance beyond ICH E5

Korea and Taiwan were able to join global registration studies

No clinical studies in China prior to first global approval

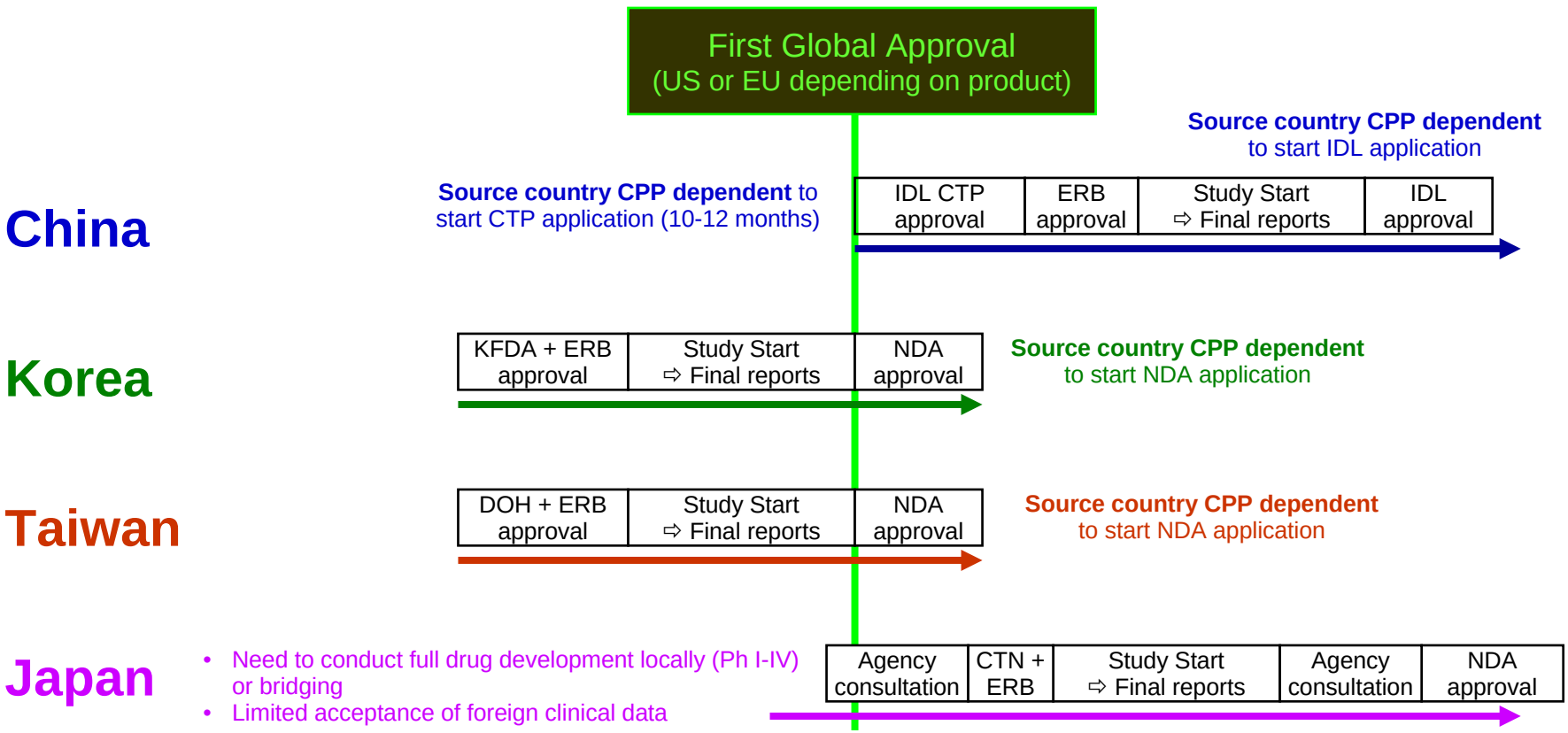
Less developed clinical trial and GCP infrastructure

Full development or bridging in Japan

East Asian drug lag!

East Asia Past …

Individual Regional Strategy



CPP: Certificate of Pharmaceutical Products; CTN: Clinical trial notification; CTP: Clinical trial permission; DOH: Department of Health; IDL: Import drug license; NDA: New drug application

Lilly East Asia Past…

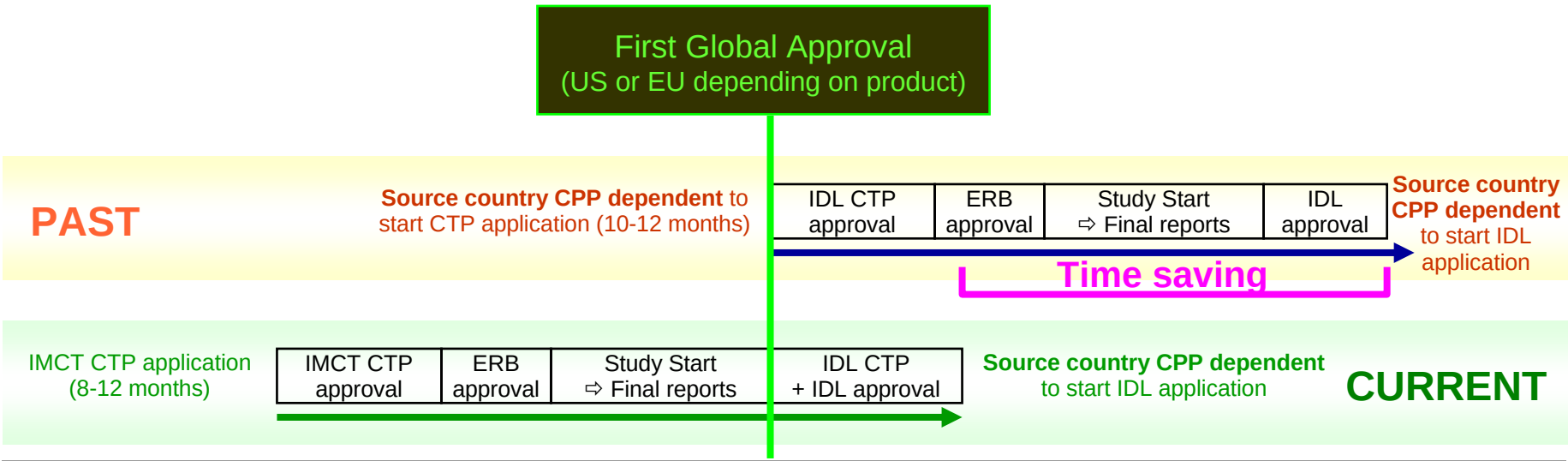
NME approval lag (years):

Product	US or EU	Taiwan	S. Korea	China	Japan	Strategy
Prozac	Dec 87’	+2.2	+2.2	+3.0	N.A.	Individual country trials
Gemzar	Oct 95’	+1.8	+3.1	+3.1	+3.2	Taiwan joined global trials. Individual trials for all others
Zyprexa	Sep 96’	+2.1	+2.0	+2.1	+3.2	Korea and Taiwan joined a global trial, China and Japan stand alone trials
Evista	Dec 97’	+2.0	+3.5	+5.0	+7.0	Taiwan joined a global trial. Individual trials for Korea and China. Bridging for Japan.
	Avg.	***+2.0***	***+2.7***	***+3.3***	***+4.5***	

Larger drug lag in China and Japan

Present…China

Changes to regulatory requirements and practice

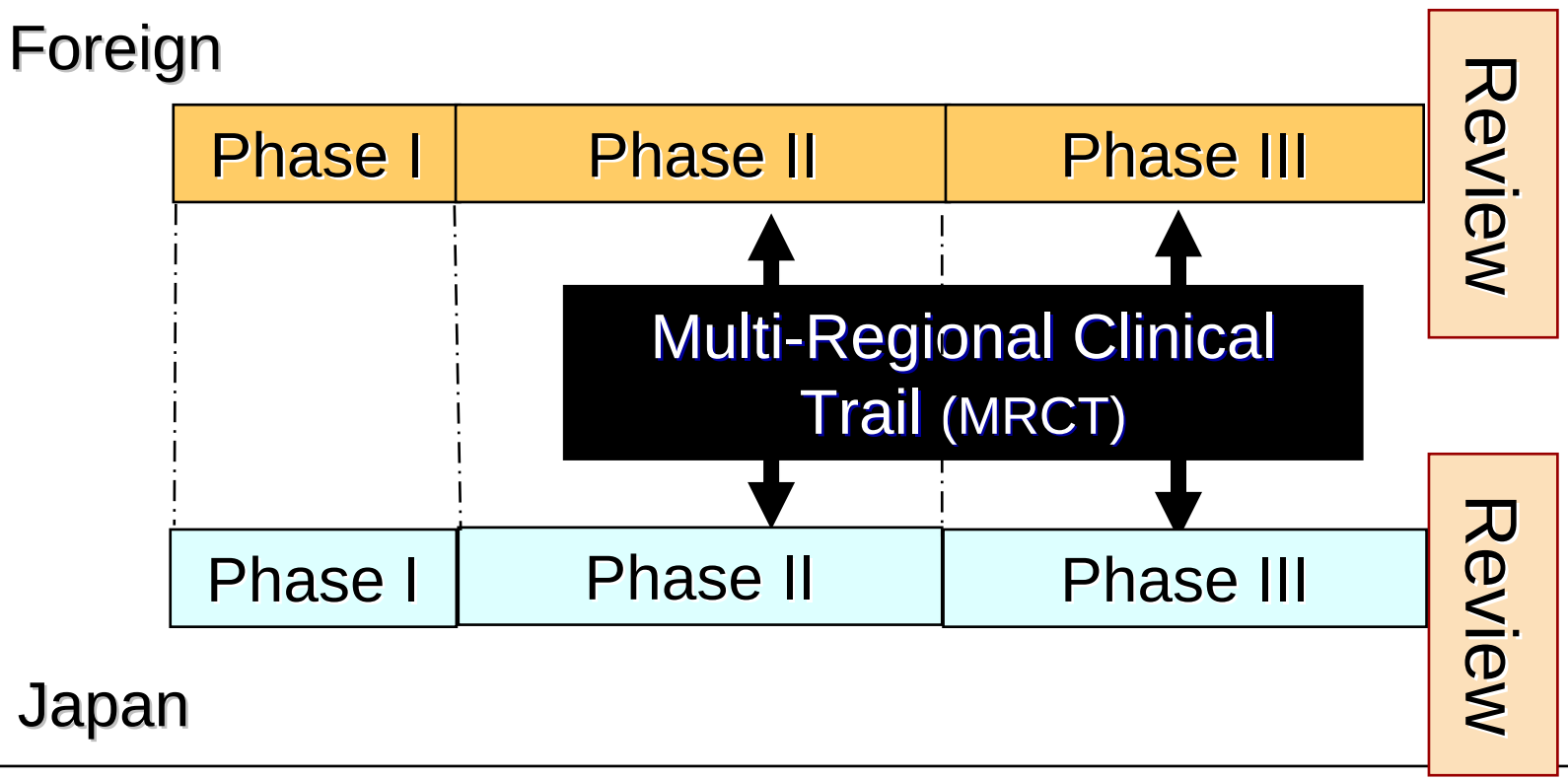


- Initiate IMCT after global Phase IIb and prior to first global approval
- Include at least 2 additional regions (excluding Taiwan)
- Opportunity to reduce drug lag equivalent to trial approval and duration

International Multi-country Clinical Trial (IMCT)

Present …Japan

- Real examples of foreign data acceptance and product approvals
- Established Q&A guideline for global studies including Japan
- PMDA/MHLW are actively promoting MRCT and simultaneous development



Lilly Asia IMCT Experience

Asian IMCTs with China (without Japan)

- China requires a larger patient allocation
- Single phase III studies for registration

Compound	Country	Actual Patient No	Trial Last Patient Visit
Byetta Type II Diabetes	China	242	21-Apr-07
	Korea	80	
	India	99	
	Taiwan	51	
Cymbalta Depression	China	244	12-Jun-05
	Korea	123	
	Taiwan	68	
	Brazil	43	
Strattera ADHD	China	242	17-Oct-04
	Korea	60	
	Mexico	28	

Lilly Asian IMCT impact…

IMCT driven drug lag reduction (years):

Product	US or EU	Taiwan	S. Korea	China
Strattera	May 04’	+1.3	+1.3	+2.0
Cymbalta	Dec 04’	+1.5	+2.5	+1.6
Byetta	Nov 06’	*+1.7 **	*+1.5 **	*+2.0 **
	Avg.	***+1.5***	***+1.8***	***+1.9***

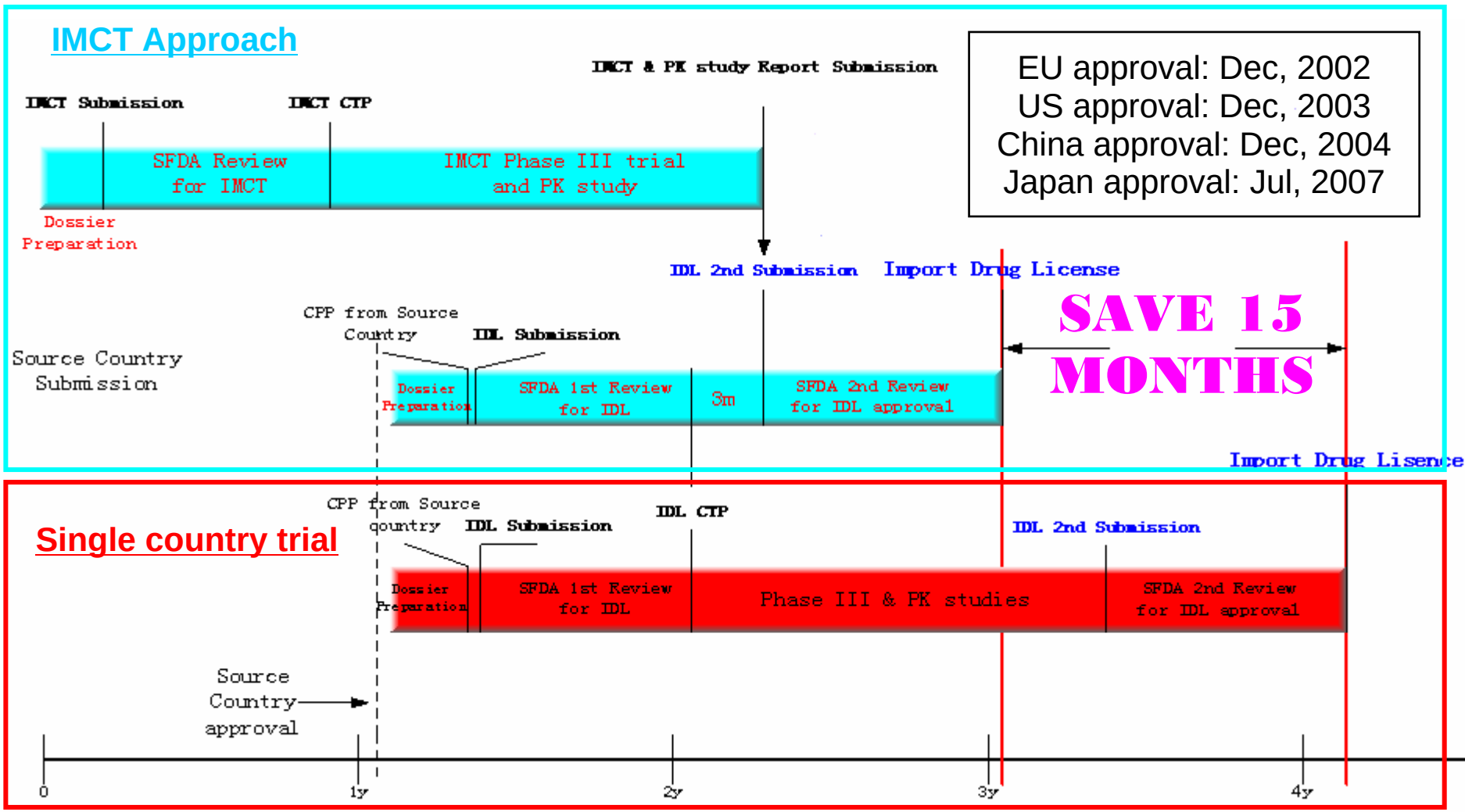
Lag near equal to regulatory approval time post source CPP

Significant lag reduction for China (+3.3 ⟶ +1.9)

* Projected approval

Present …*China in a Regional IMCT*

Example: Cialis (ED) - Earlier drug launch for China



EU approval: Dec, 2002
US approval: Dec, 2003
China approval: Dec, 2004
Japan approval: Jul, 2007

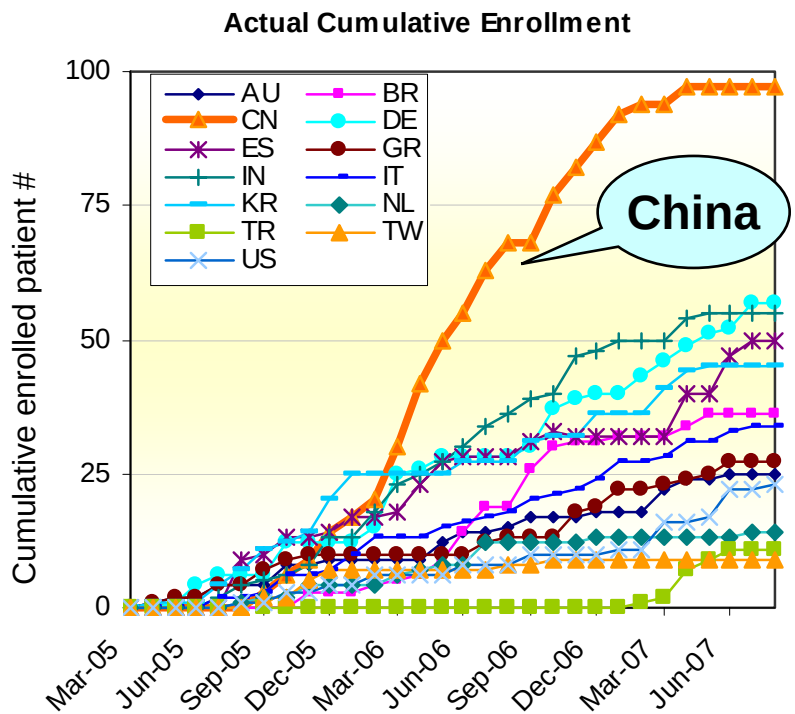
Present…*Asia Success in a Global Trial*

Increasing contribution to global studies due to high productivity

- Asia share about 12 % of patients in global US/EU registration studies (2007)
- ↑ enrollment rate & ↓ dropout with no sacrifice in quality

Example: Asian countries (especially China) in one global Oncology study

Country	Patient#	Site #	Enrolment Period (Months)	Enrollment Rate (per site per month)
AU	25	7	26.0	0.14
BR	36	4	19.8	0.46
CN	**97**	**8**	**20.2**	**0.60**
DE	57	5	25.8	0.44
ES	50	8	25.7	0.24
GR	27	5	25.7	0.21
IN	**55**	**5**	**21.9**	**0.50**
IT	34	9	23.1	0.16
KR	**45**	**2**	**25.1**	**0.90**
NL	14	4	21.1	0.17
TR	11	3	3.3	1.10
TW	**9**	**1**	**13.5**	**0.67**
US	23	12	22.7	0.08
Total	**483**	**73**	**21.2**	**0.40**



East Asia Future…

Simultaneous development including Japan

Leverage existing capability / capacity built up in Asia (China, Korea, Taiwan, Japan)

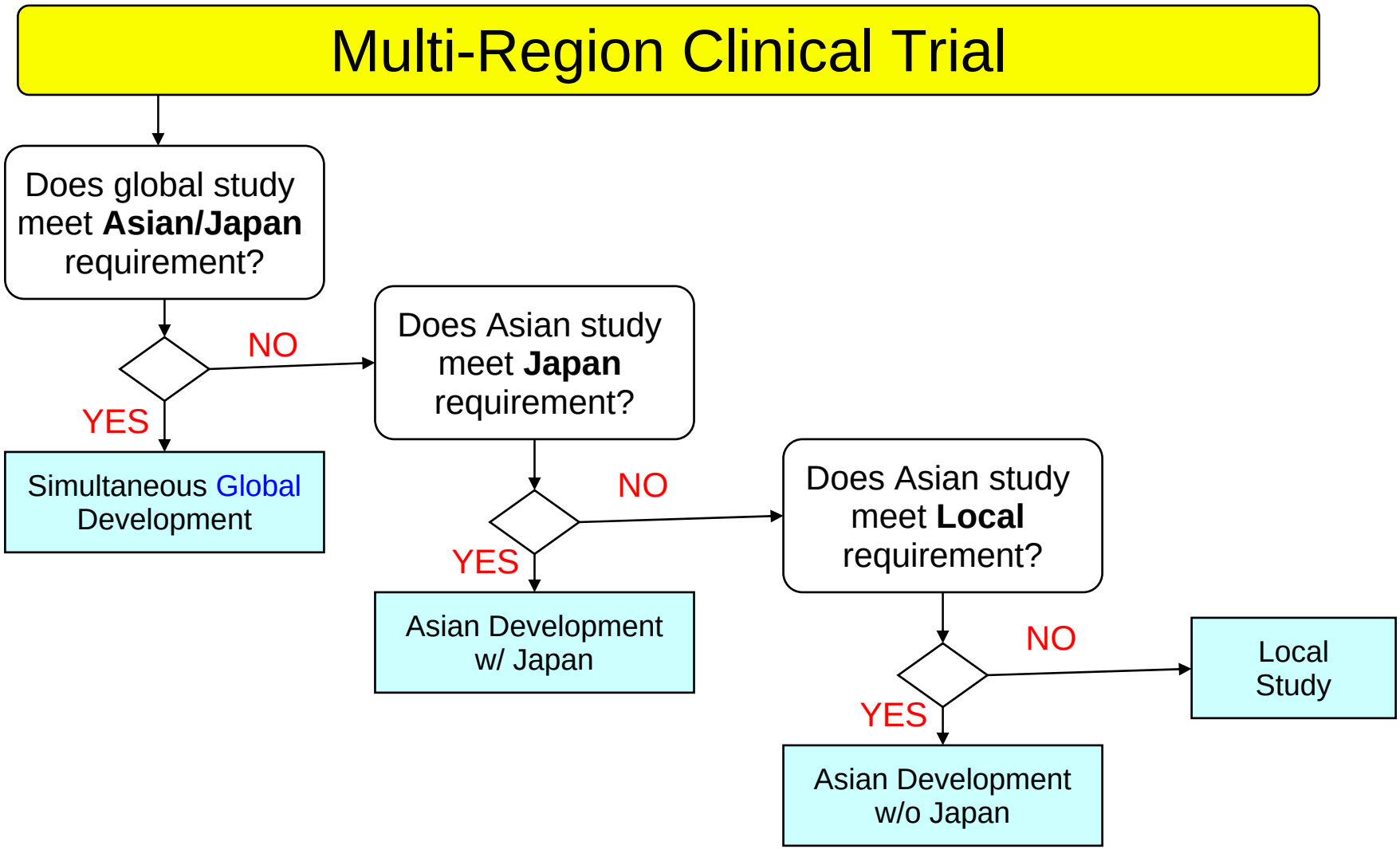
Incorporate Japanese and Chinese regulatory changes into development and clinical plans

Pooled Asian ethnicity assessments

Various options to obtain registrations in Asia

- Global or Regional IMCT
  - Global US/EU Phase II/III registration trials
  - Regional registration trials with Japan
  - Regional registration trials without Japan
- Stand alone – Local registration trial

Future…Strategy



Future…*East Asia Regional Trial*

Example: Ongoing Lilly Type II diabetes Asian registration trial

Estimated significant cost saving for Japan by joining IMCT

Asian trial without Japan

- IMCT (China + Taiwan + Korea + India)
  - 400 ~ 500 pts

Japan Stand alone trial

- Japan
  - 350 pts

Asian trial with Japan

- IMCT (China + Taiwan + Korea + India + Japan
  - 670 (including 150 pts for Japan)

<u>Implication for Japan to join</u>:

- **↓ Sample size (~ 200 patients less)**
- **≥ 40% ↓ in study budget, ≥ 30 % ↓ in human resources cost**
- **↓ Enrollment period**
- **↓ Time to trial completion**

= More rapid access for patients!

Future…*East Asian Global Trials*

Lilly Global CT (with Japan):

Study A	
Status	Completed
Therapeutic Area	PAH
# of countries	10
Total # of patients	406
# of patients in Japan (no other East Asian countries)	26
% of Japanese	6.4

Study B	
Status	Ongoing
Therapeutic Area	Cancer NCE
# of countries	23
Total # of patients	460
# of patients in East Asia (Japan, Korea, Taiwan and China)	100-110
% of East Asian Population	21-24

Global with Japan **Global with East Asia**

Global data package
Simultaneous global submission

Future…… *Asia in Global / Regional Trials*

Common development factors:

Faster access to new drugs for patients with lower development cost

	China	Taiwan	Korea	Japan
Sample Size	No Change (As per CN SFDA's requirement)	↓ Fewer patient required in a global vs. regional study	No Change (Country target to meet KFDA requirement)	↓ East Asia contributes patients to meet PMDA requirement
Study conduct	↓ Share project management resources	↓ ↓patient number share project management resources	↓ Share project management resources	↓ ↓patient number ↓higher study cost share project management resources
Drug Launch Timeline	Significantly earlier (study initiation before 1st global approval)	Earlier (participating in global trials or with bridging waiver)	Potentially earlier (easier to secure development resource)	Significantly earlier (↓ enrollment period due to ↓ patient no)

Major Challenges Facing Drug Development

- Dissatisfaction with current efficacy/safety profiles of marketed drugs – **"the efficacy/tolerability/safety gap"**
- Payers, patients want **real-world** effectiveness, outcomes and safety data
- New drugs **cost too much, take too long** to develop
- Public **trust is shaken** in medical data

……Major changes are **urgently** needed in the traditional drug development paradigm.

Future…*Challenges*

Regulatory Requirements/practice

Japan:

- Phase I in Japan almost always required
- Full development in Japan philosophy: (Ph I-IV), Parallel vs. Simultaneous
- Lengthening NDA cycle time

China:

- CTP approval required before ERB application
- 4X longer CTP approval time: Difficult to align multi country trial start time
- Full development trials in China for biological drugs: Ph I-III
- Trial, country & site specific study reports
- Predetermined patient number (Phase III) regardless of development plan:
  - Chemical drug: = 100 completers/arm + statistical power
  - Biological drug: = 300 completers/arm + statistical power
- Need source country approval to complete the NDA application process
- Limited development consultation process

Future…*Challenges*

Regulatory Requirements/practice

Korea:

- Bridging study requirement: Need a global study of similar study design
- Insufficient guidance for ethnicity assessment (PK/PD vs. Phase III)
- Increasing emphasis on Korean specific data
- Limited development consultation process
- Need source country approval to complete the NDA application process

Taiwan:

- CPP dependent drug approval process
- Increasing hurdle to obtain bridging consultation approval
- Increased emphasis on Taiwan specific data
- CMC and GMP requirements beyond US/EU

Future…*Challenges*

Clinical Infrastructure

Increasing competition running clinical trials

- Patient recruitment amongst PhRMA companies
- Increasing company and trial site staff turnover
- Potential quality risk due to new business model (clinical contracting)

Integration and logistics for Multi-Regional Trials

- Expertise for project management
- Varying regulatory requirements amongst countries
- Varying local standard medical practice amongst countries
- Comparator vs. placebo preferences
- Difficult to export DNA / plasma samples (China)

Future…*Opportunities*

Regulatory Requirements/practice

Continually evolving flexibility for product registration efficiency and acceleration

- Integrate with US and EU development modernization

Increased collaboration and alignment among East Asian regulators

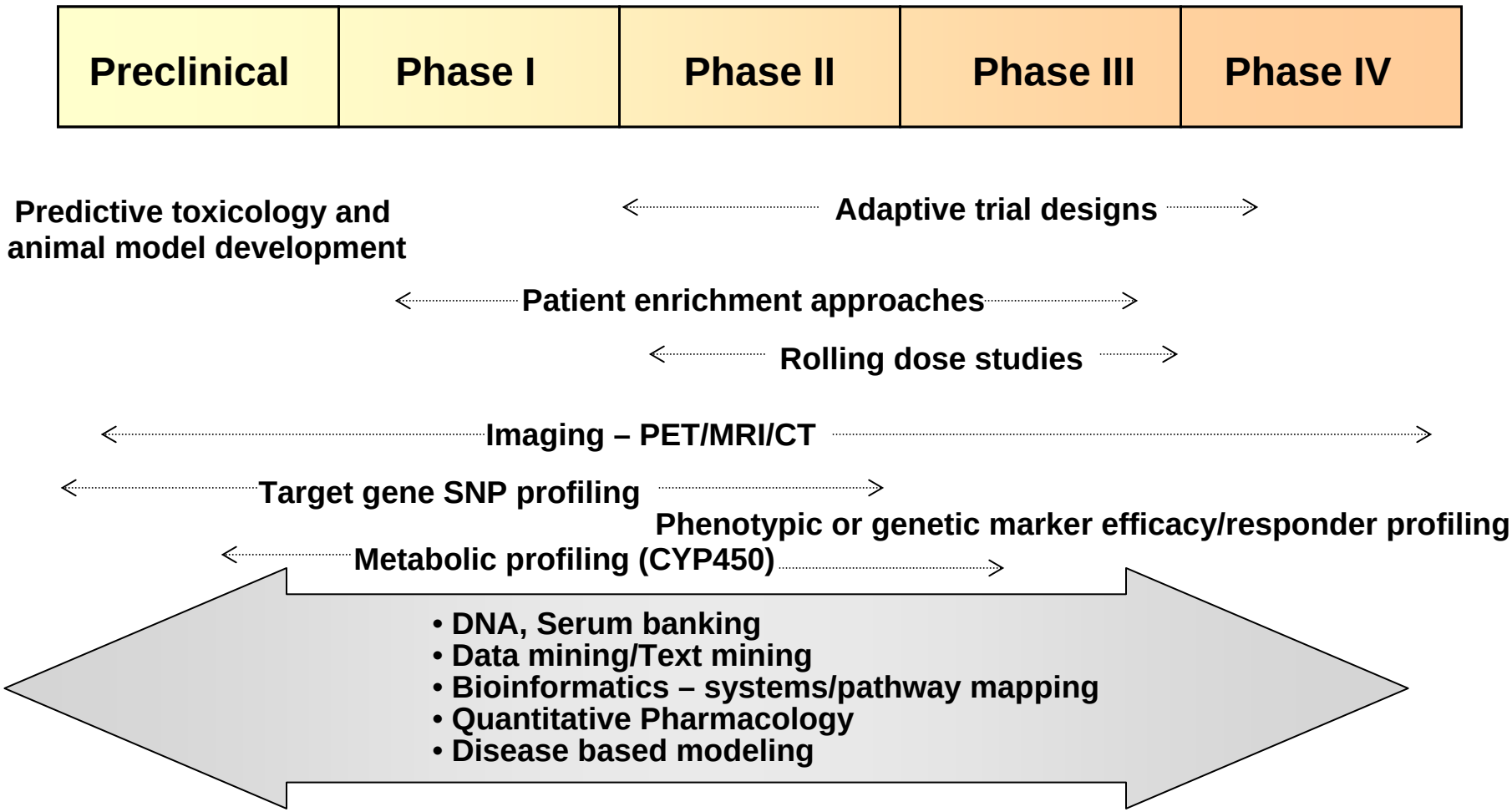
Increased acceptance of common East Asian ethnicity assessments

Shorter CTP approval timeline for “Innovative products” (China)

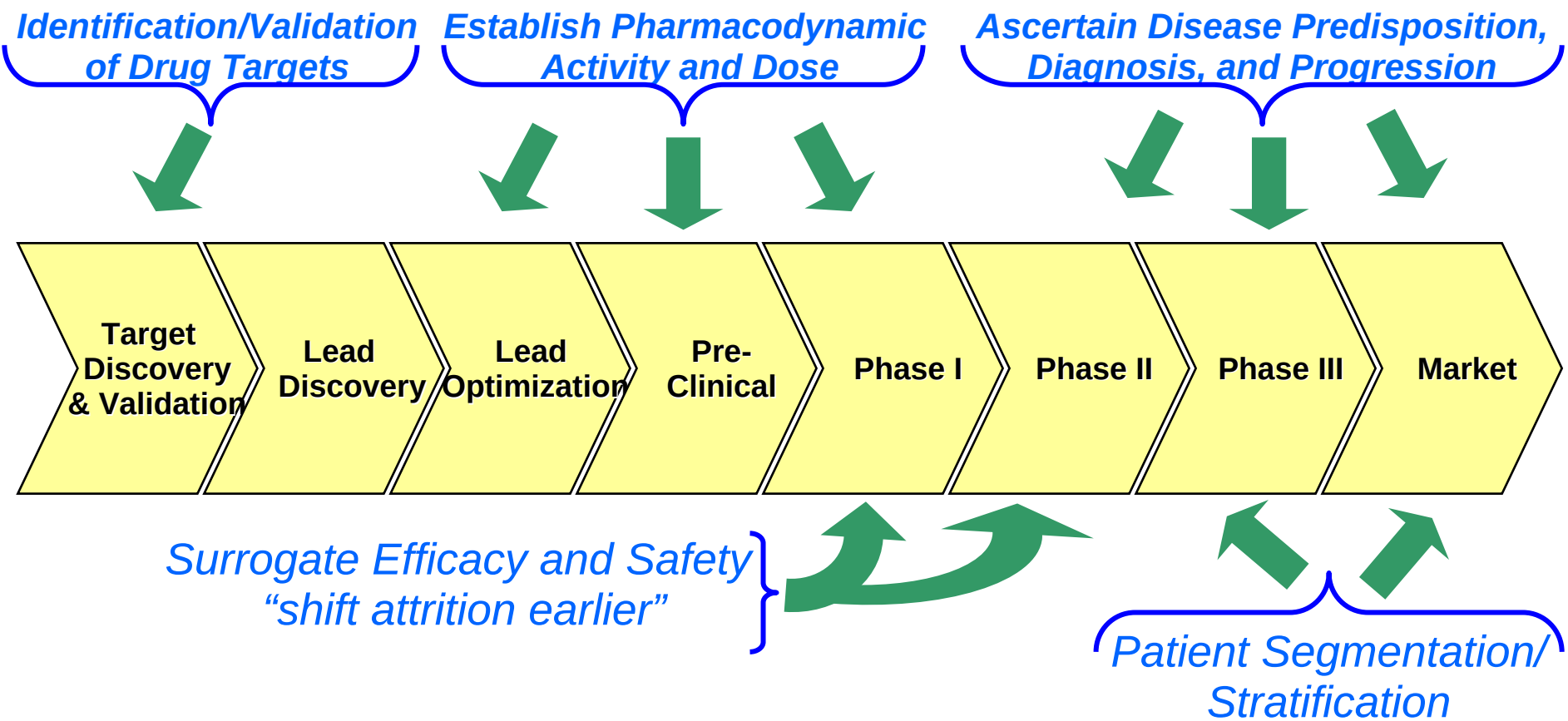
Removal of predefined patient allocation targets (China, Taiwan)

Increased opportunity for development consultation (China, Korea)

What Are We Doing Differently?



Biomarkers: Impact Across the Entire Drug Discovery/Development Value Chain



Biomarkers can improve both R&D productivity and help define the "right drug for the right patient"

Future…*Opportunities*

Clinical Infrastructure

Favorable clinical research environment

- Large patient pool
- Highly competitive investigator fee & labor cost comparing US, EU
- Well trained & highly motivated investigators
- Excellent physician-patient relationship
- Dedicated & well trained Lilly medical staff

Large unmet medical needs

- Increasing level of focus & investment in R&D by companies and governments
- Increasing allocation of global US/EU registration trials to Asia

Increasing growth of GDP & PhRMA market, especially China

Drug Development's Key Challenge – Addressing Unmet Medical Needs with a Sense of Urgency

- **In the last 40 minutes, there have been…**

10	new diagnoses of schizophrenia
132	deaths due to cancer
20	osteoporosis related hip fractures
1296	cases of anxiety disorder diagnosed
1524	surgical procedures requiring pain treatment
72	deaths due to cardiovascular disease

……patients are waiting !

Ways Forward

- Collaboration
- Creativity in design/review
- Continuous modification
- Communication

Thanks to each & all of you !!