Introduction to Clinical Trial

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Clinical Trial/Study

Wikipedia

Clinical trials are sets of tests in **medical research** and **drug development** that generate safety and efficacy data for **health interventions** (e.g., drugs, diagnostics, devices, therapy protocols).

ICH GCP E6

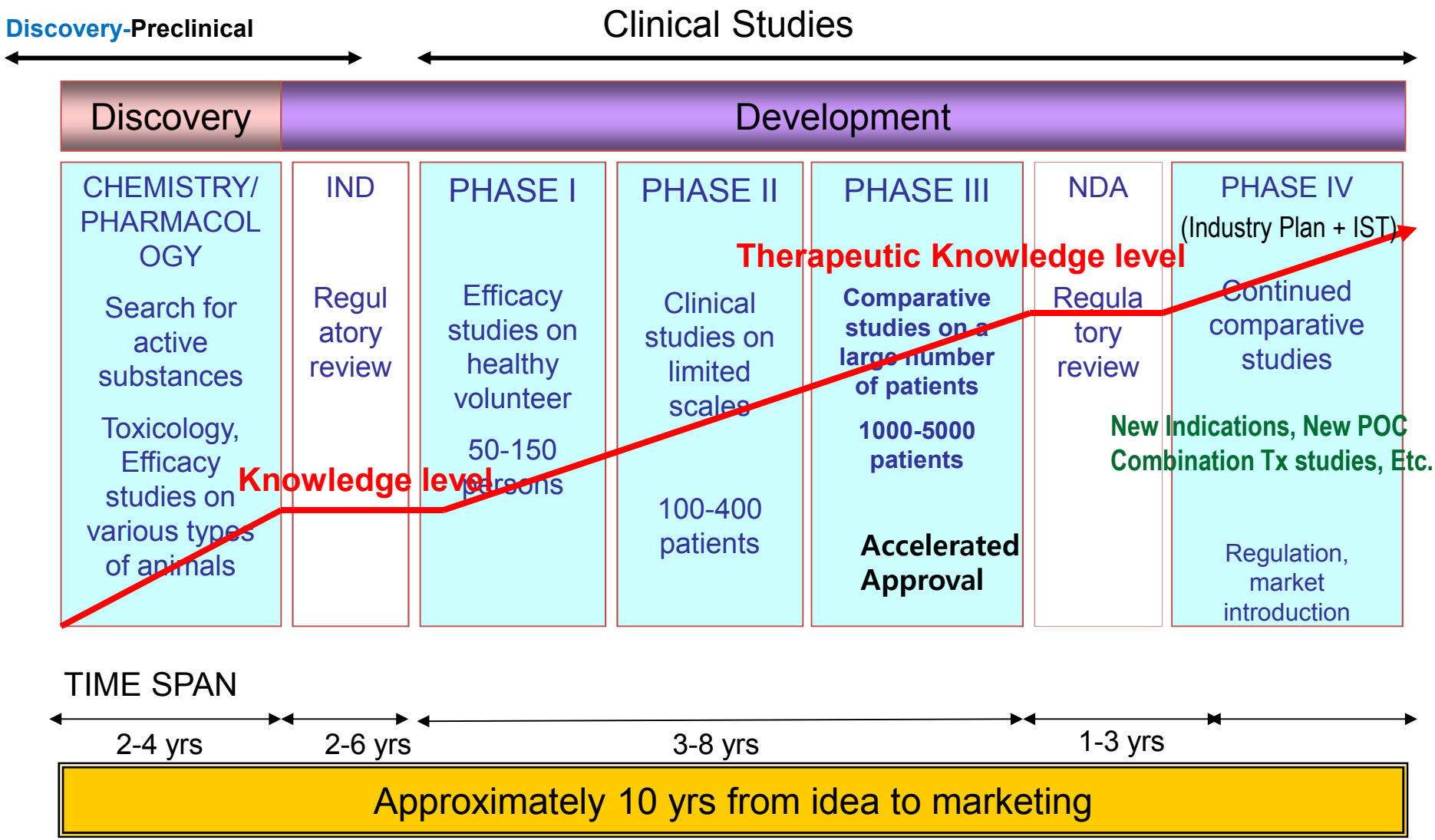
Clinical Trial/Study is an investigation in **human subjects** intended to discover or verify the pharmacokinetic, pharmacodynamic, pharmacological, clinical effects of an **investigational product(s)**, and/or to identify any adverse reactions to an investigational product(s), with the object of ascertaining its safety and/or efficacy.

Method of Medical Research

- **Hierarchy of Evidence**

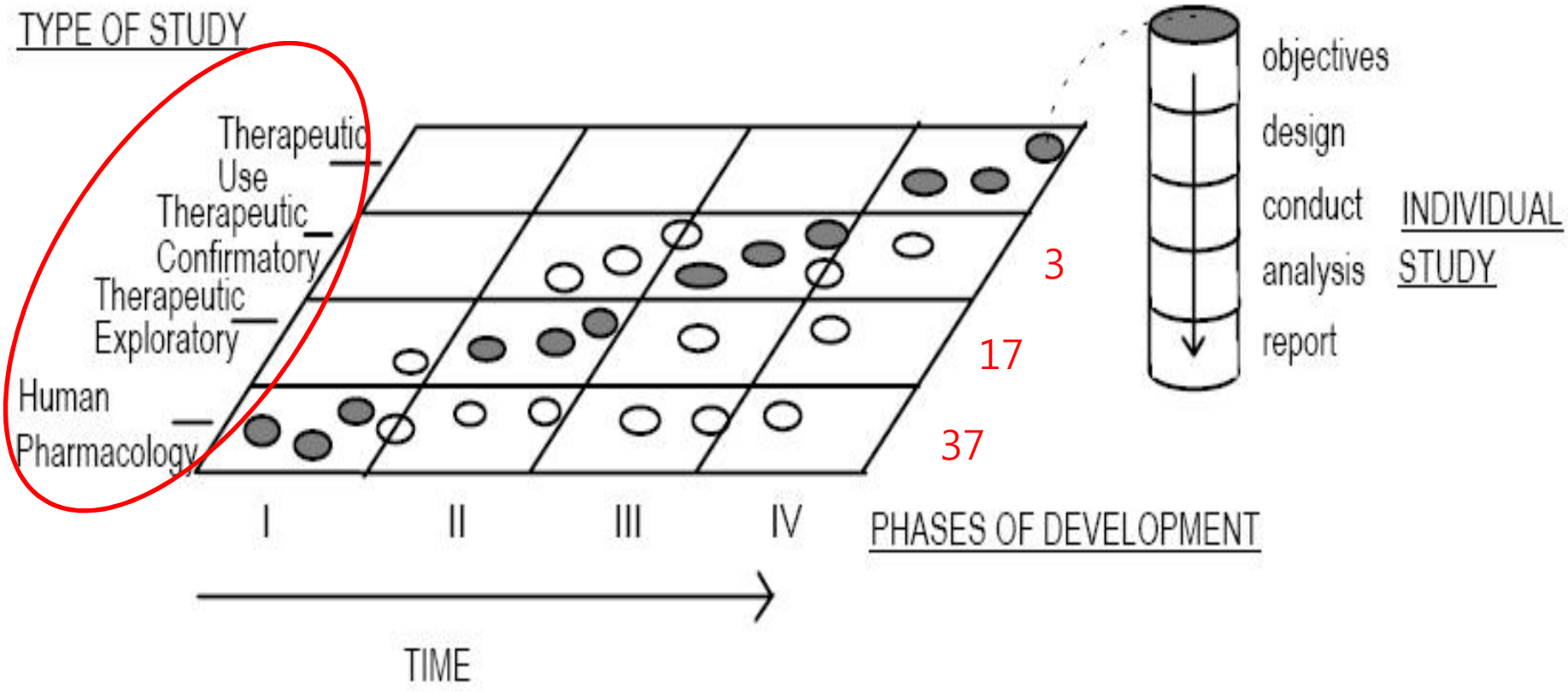
Evidence	Type
weak	Non-clinical trial (In vitro/ex vivo/animal)
	Case report (환자 사례 보고)
	Case series study (환자군 연구)
	Cross-sectional study (단면조사 연구)
	Case-control study (환자-대조군 연구)
	Cohort study (코호트 연구)
Strong	Randomized clinical trial (무작위배정 임상시험)
	Systemic review/ Meta-analysis (체계적 리뷰/메타분석)

Drug Development Process



Ref: JW Sohn, AZ

Development Phase and Type of Study



- ● **Usually conducted in a certain phase of development**
- ○ **May be conducted in that phase, but are less usual**

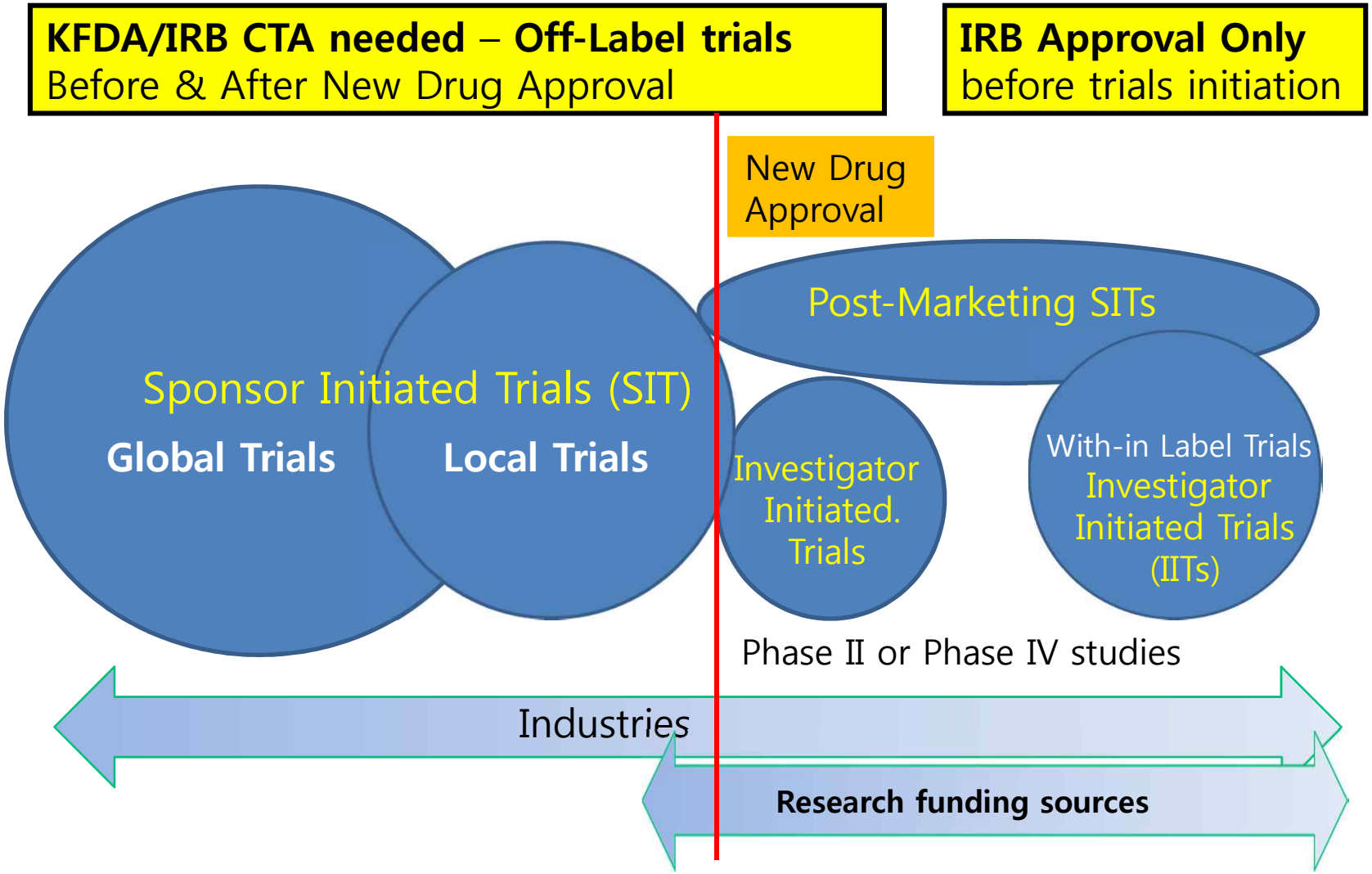
ICH E8: General considerations for clinical trials

Classification Clinical Studies According to Objective

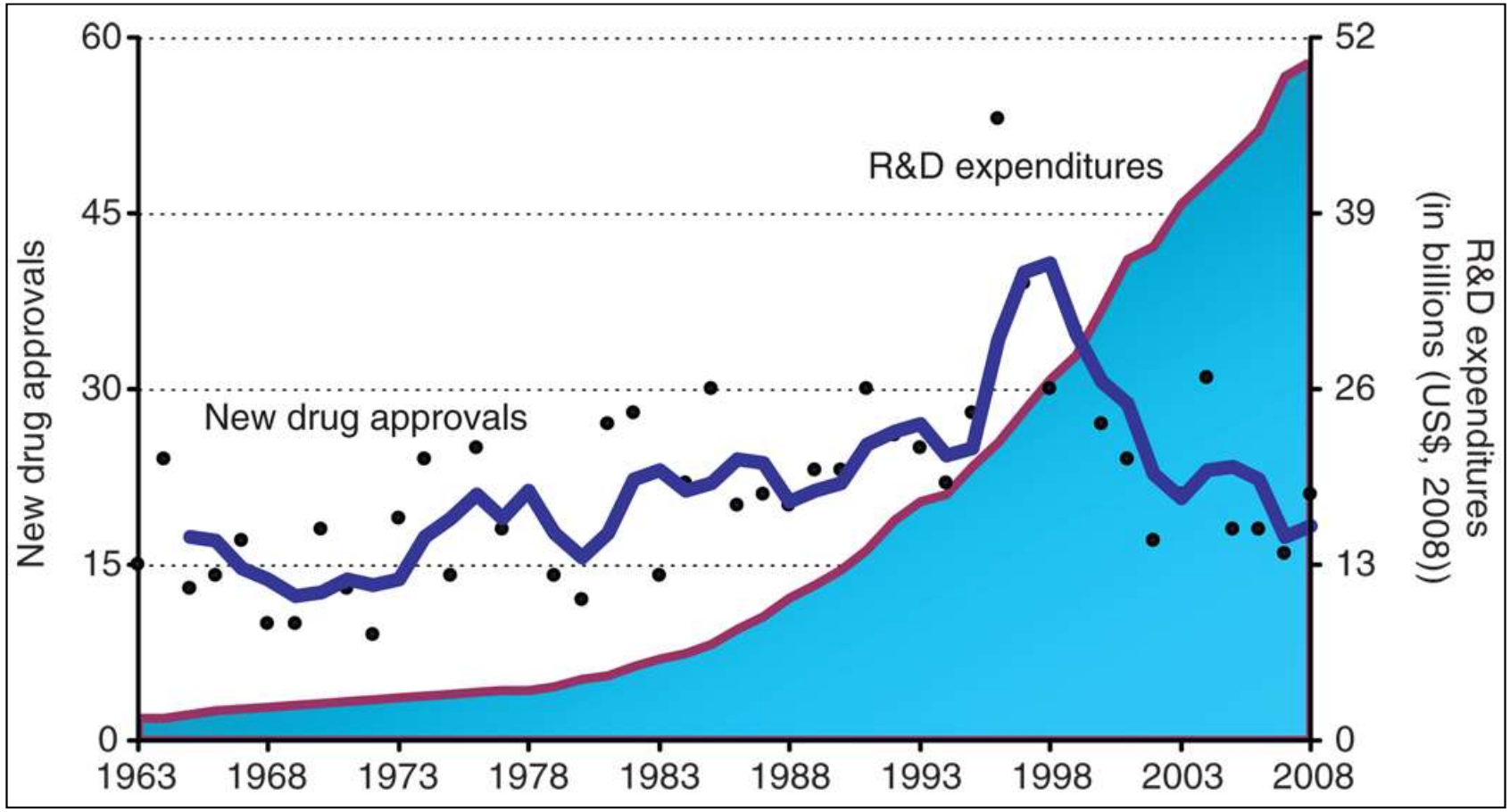
Type of Study	Objective of Study	Study Example
Human Pharmacology	•Tolerability •PK/PD •Drug metabolism •Drug interaction	•First-in-human •Single/Multiple dose of PK/PD •Drug interaction
Therapeutic Exploratory	•Targeted indication •Dosage regimen •Basis for confirmatory study design	•Earliest trials of relatively short duration in well-defined narrow patient populations •Dose-response exploration
Therapeutic Confirmatory	• Confirm efficacy • Establish safety profile • Dose-response relationship • Basis for assessing the benefit/risk relationship to support licensing	• Adequate, and well controlled studies to establish efficacy • Randomized parallel dose-response studies • Clinical safety studies • Mortality/ morbidity outcomes • Large simple trials • Comparative studies
Therapeutic Use	• Benefit/risk relationship in general or special populations • Identify less common adverse reactions • Refine dosing recommendation	• Comparative effectiveness • Mortality/morbidity outcomes • Studies of additional endpoints • Large simple trials • Pharmacoeconomic studies

ICH E8: General considerations for clinical trials

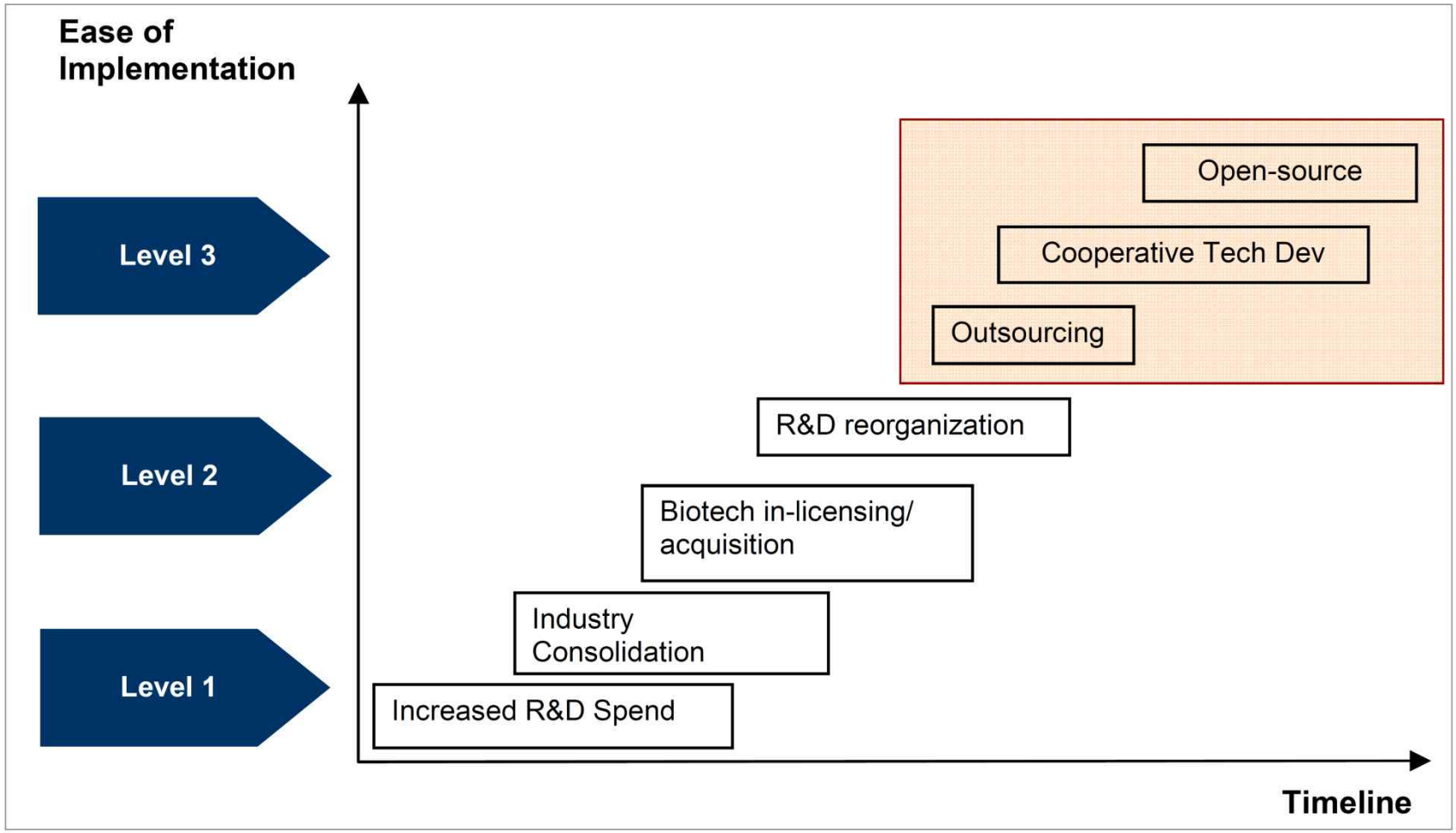
Clinical Trials Areas (gathering therapeutic evidence)



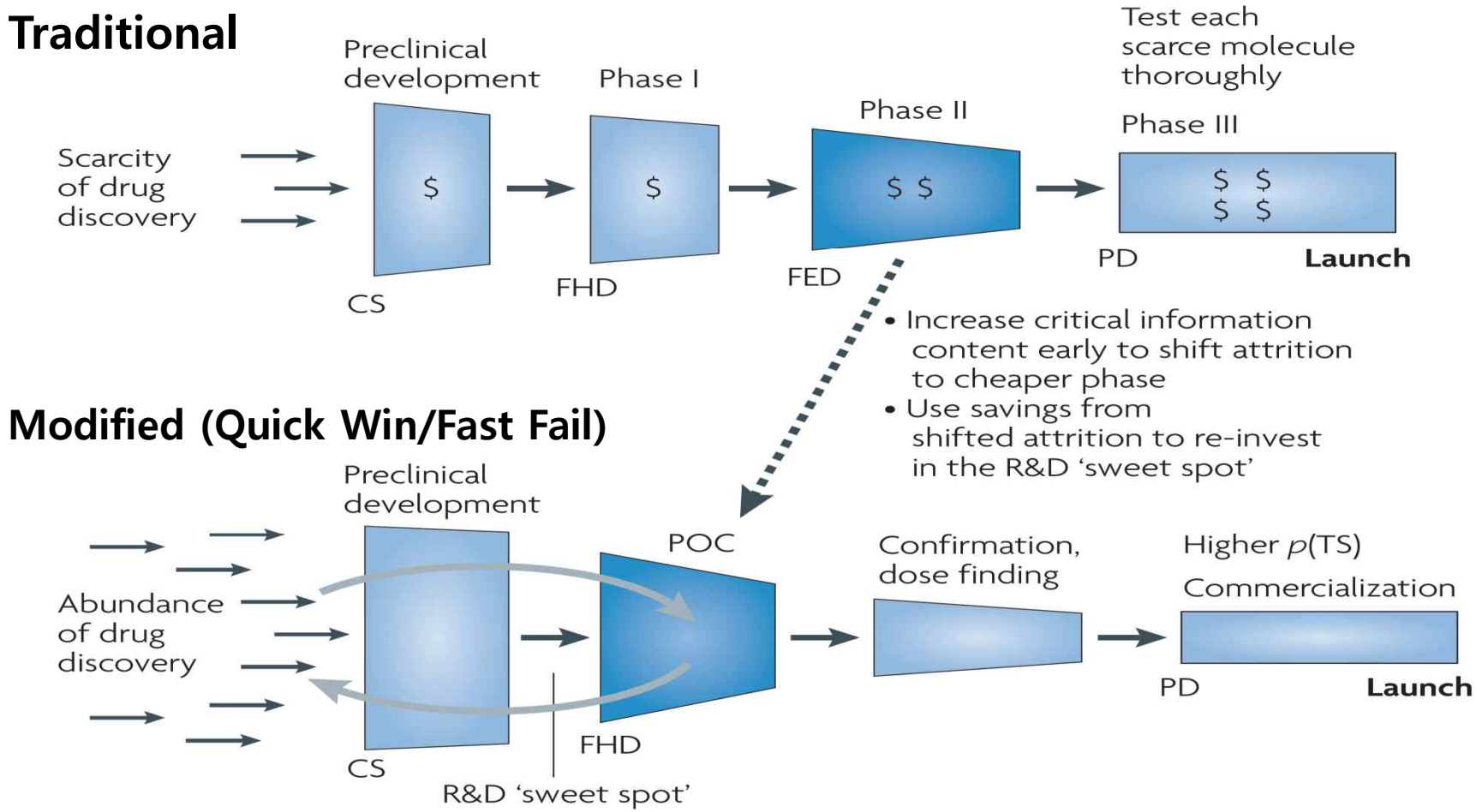
Declining R&D Productivity



Pharma's Strategies for R&D



New Paradigm of Drug Development



CS, candidate selection; FED, first efficacy dose; FHD, first human dose; PD, product decision

- Nature Review/Drug discovery 2010. 3

Example: DPP-IV inhibitor

- Typical: HbA1c, FPG
- PoC: DPP-IV activity, GLP-1, PK in DM pts

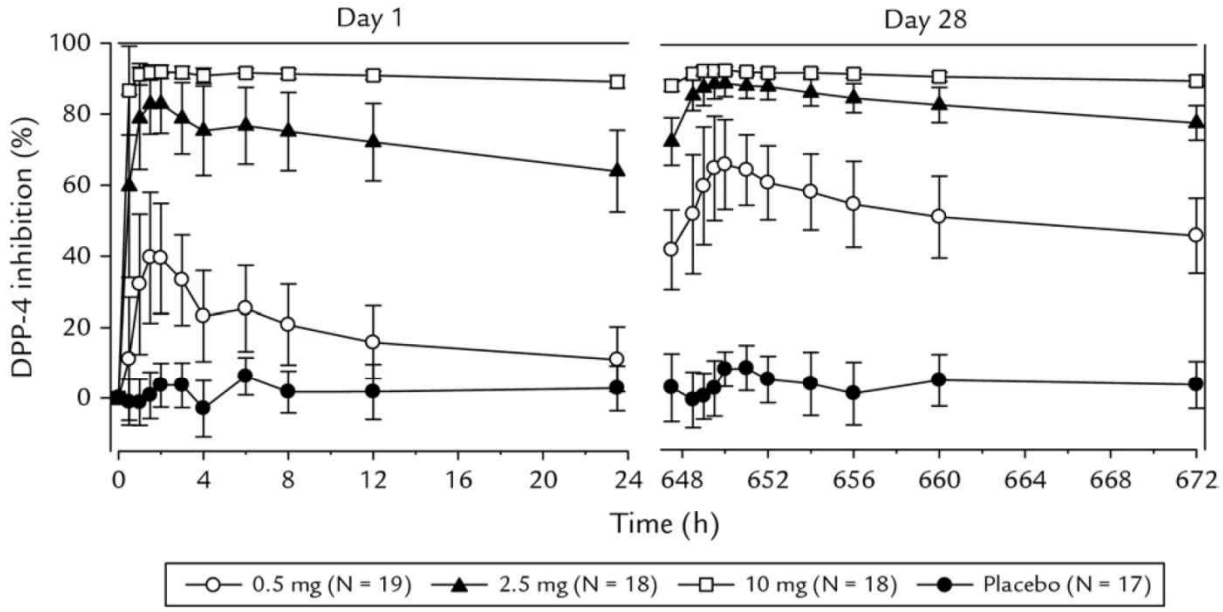


Figure 2. Mean (SD) percent inhibition of plasma dipeptidyl-peptidase-4 (DPP-4) activity after single oral doses of linagliptin (0.5, 2.5, 10 mg) and placebo once daily in male and female Japanese patients with type 2 diabetes mellitus (left panel: day 1), and after multiple dosing (right panel: day 28).

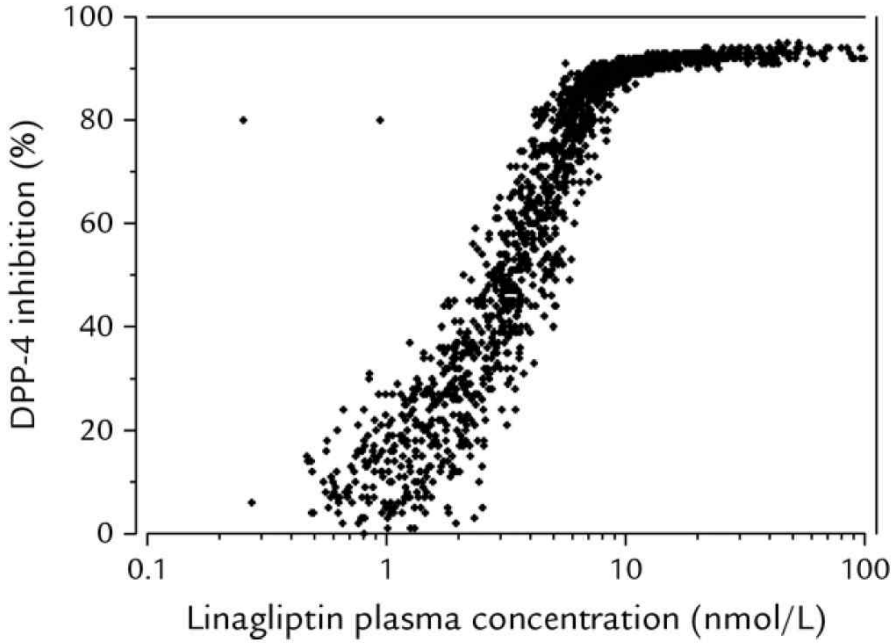


Figure 3. Scatterplot of the correlation between percent inhibition of plasma dipeptidyl-peptidase-4 (DPP-4) and plasma concentrations of linagliptin after multiple oral doses (0.5, 2.5, and 10 mg/d for 28 days) in male and female Japanese patients with type 2 diabetes mellitus.

Table III. Mean (SD) maximum inhibition of plasma dipeptidyl-peptidase-4 (DPP-4) activity (maximum pharmacodynamic effect and maximum pharmacodynamic effect at steady state) and the plasma DPP-4 inhibition 24 hours after dosing on days 1 and 28.

Dose	E_{max}, %	E_{24}, %	$E_{max,ss}$, %	$E_{\tau,ss}$, %
Placebo	8.9 (3.6)	2.8 (6.4)	9.7 (5.1)	2.4 (8.1)
0.5 mg	42.1 (17.5)	11.0 (9.2)	66.7 (12.0)	45.8 (10.6)
2.5 mg	84.7 (7.9)	63.9 (11.5)	89.6 (3.8)	77.8 (4.9)
10 mg	92.5 (1.2)	89.1 (1.8)	92.9 (1.0)	89.7 (1.4)

E_{24} = effect at 24 hours; E_{max} = maximum effect; $E_{max,ss}$ = maximum effect at steady state; $E_{\tau,ss}$ = effect at 24 hours at steady state.

Phase 0 trial (Exploratory IND)

- is conducted prior to the traditional dose escalation, safety, and tolerance studies,
  based on a more limited preclinical data set than that required for a traditional Phase 1 study
- involves **very limited human exposure**
  : 1/100 NOAEL (microdosing), <7 days,
- has **no therapeutic intent**

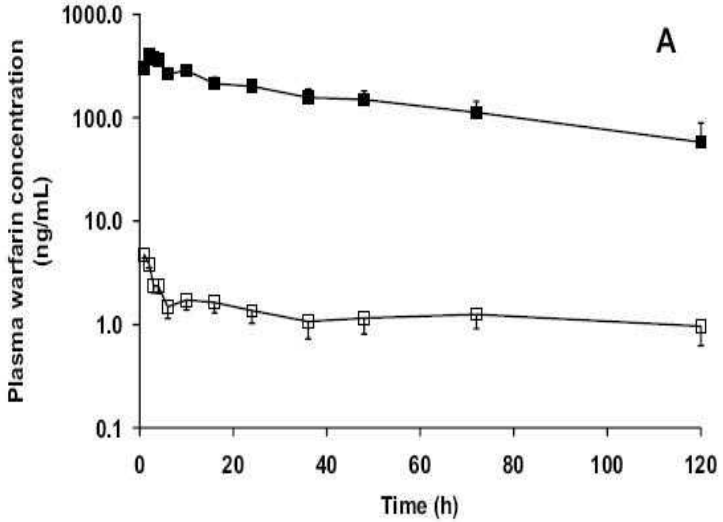
For example,

- Clinical studies of pharmacokinetics or imaging
- Clinical trials to study pharmacological effects
- Clinical studies of MOAs related to efficacy

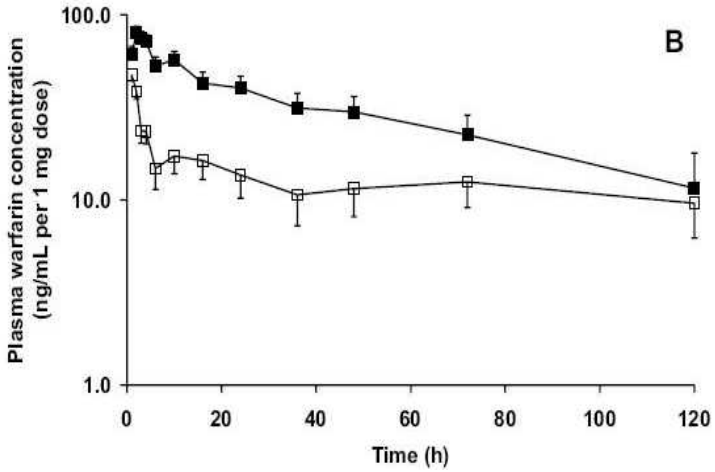
"Guidance for Industry, Investigators, and Reviewers, Exploratory IND Studies" (US FDA)

Microdosing Study

Log scale



Normalized to 1-mg dose



Treatment (n=6)	T_{max} (h)	C_{max}/D (ng/mL)	AUC_{all}/D (ng*h/mL)	AUC_{inf}/D (ng*h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	Vd/F (L)
100 µg Oral	1.12	50.4	1570	5710	274	0.17	67.3
5 mg, Oral	1.70	98.6	3230.4	4160.2	48.6	0.26	17.9

Clin Phar & Ther 80 (3), Sep 2006

Trends in the Globalization of Clinical Trials

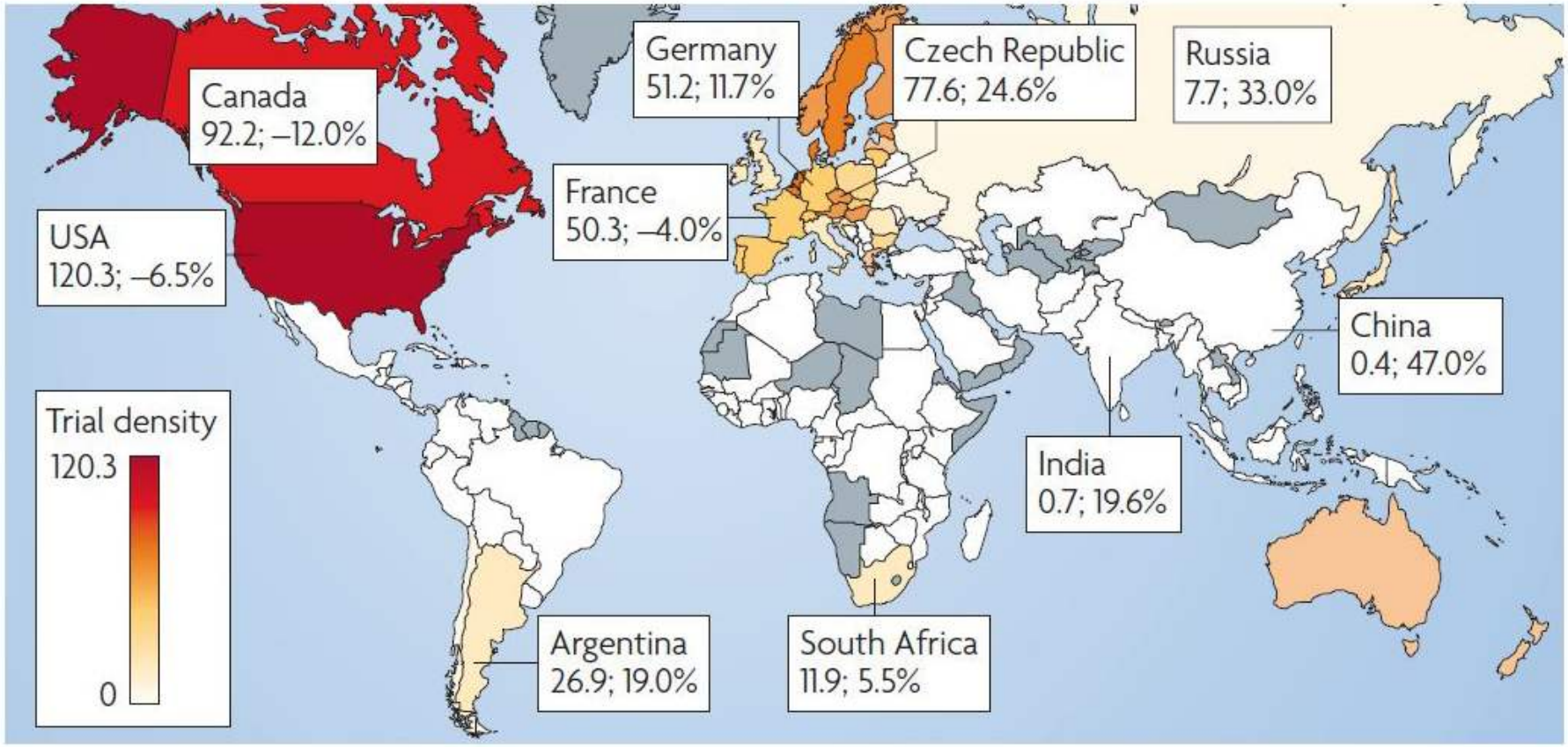
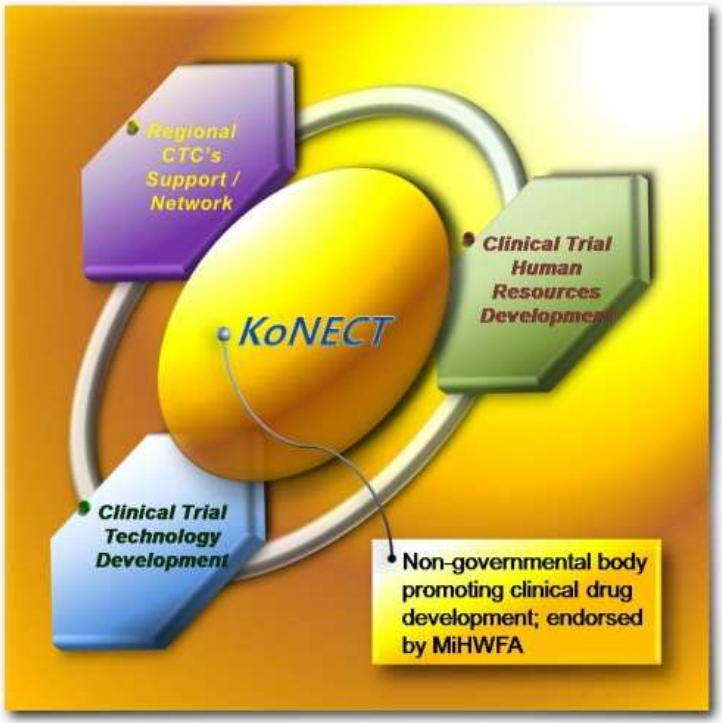


Figure 1 | **Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide.** Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in percent is shown for selected countries. The countries in grey had no actively recruiting biopharmaceutical clinical trial sites as of 12 April 2007.

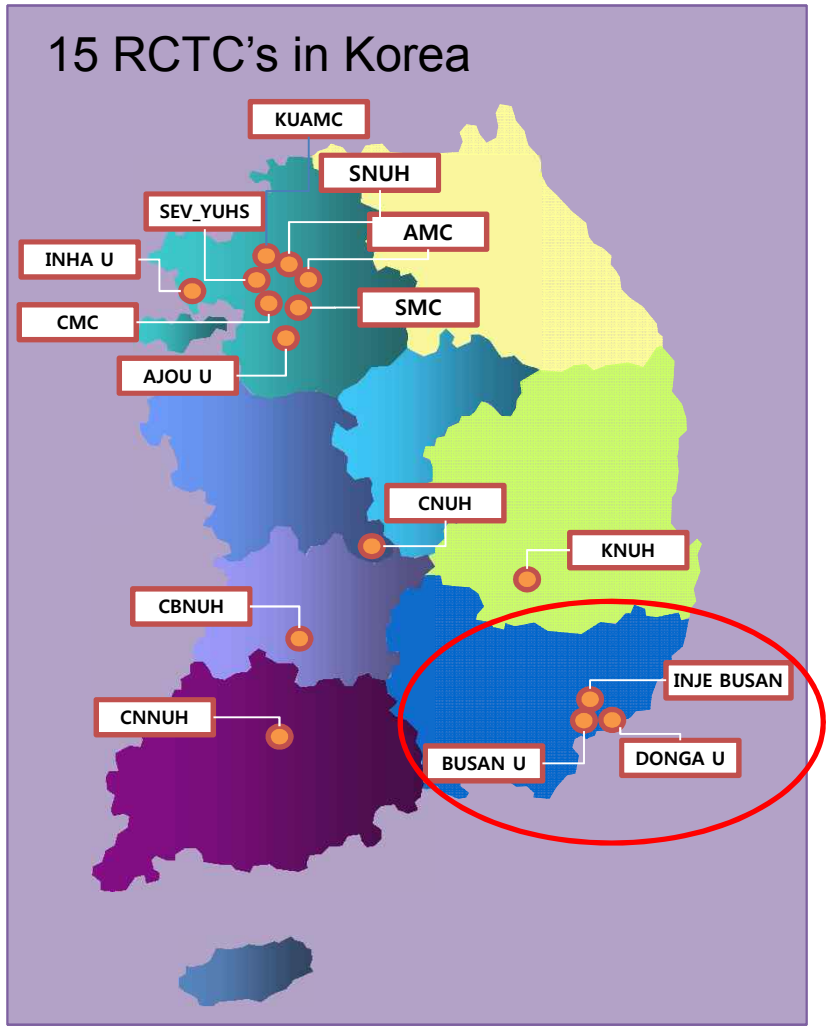
- Nature Review/Drug discovery 2008. 1

Governmental Initiatives to Support Clinical Research in Korea

INITIATIVES BY MOHW(2004 -): KoNECT (2007 -)

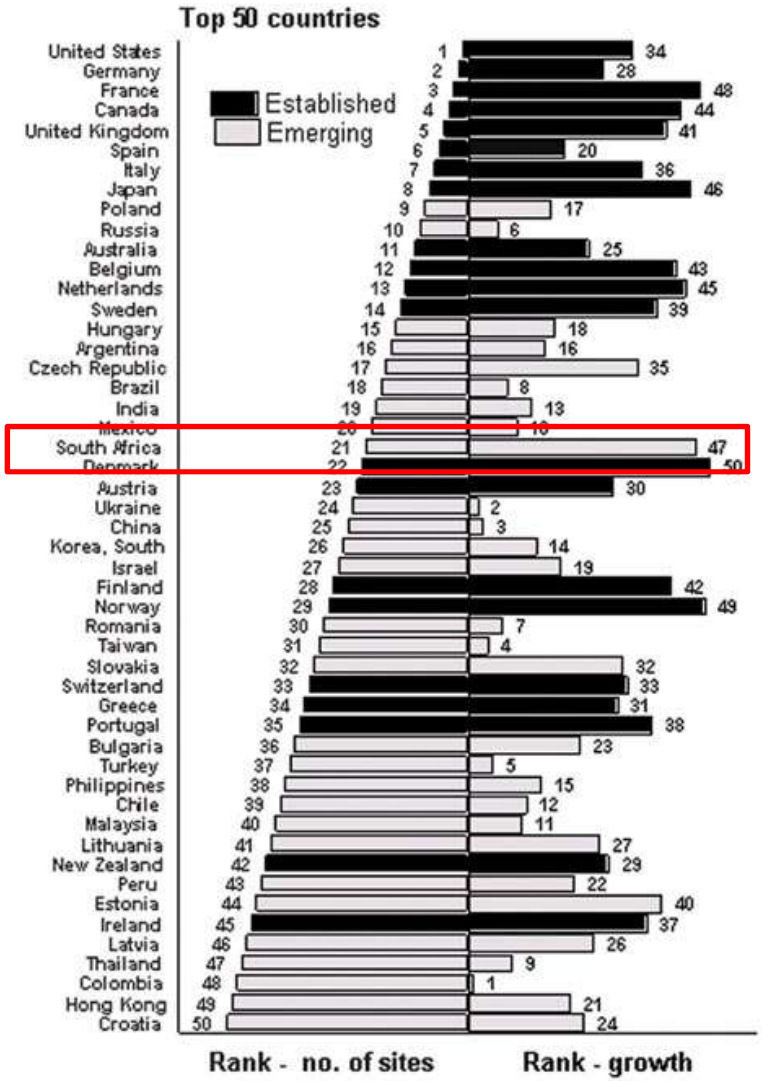


Clinical Trials Information Center
- National Statistics in Clinical Trial Area
- Improving Clincal Trial Efficiency
- Improve Public Awareness; Provide Info
- Improving Safety of Trial Subjects
- Human Resources and Gloabal Network Mangement, International Collaboration



Globalization of Clinical Trials

<2002~2006>



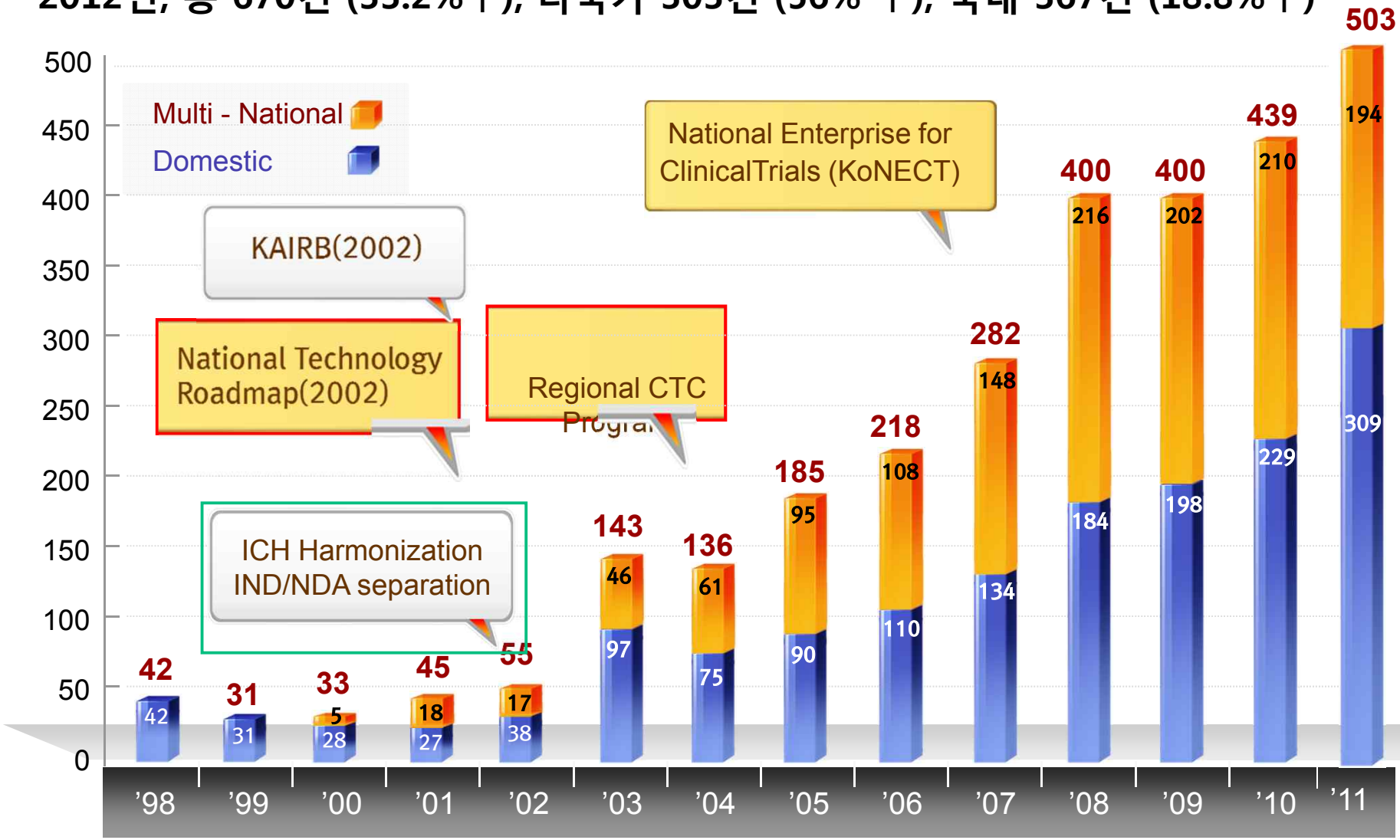
- Nature Review/Drug discovery 2008. 1

순위	2006		2010		2006~2010	
1	United States	1734	United States	2053	United States	11181
2	Germany	614	Germany	611	Germany	3433
3	Canada	492	Canada	384	Canada	2531
4	United Kingdom	449	United Kingdom	384	United Kingdom	2401
5	France	440	France	367	France	2241
6	Spain	364	Italy	281	Spain	1909
7	Italy	363	Spain	281	Italy	1834
8	Poland	301	Belgium	280	Belgium	1600
9	Belgium	287	Japan	272	Poland	1453
10	Australia	278	Korea, Republic of	236	Australia	1360
11	Netherlands	264	Poland	203	Netherlands	1305
12	Russian Federation	223	India	189	Russian Federation	1140
13	Czech Republic	222	Australia	188	Sweden	1111
14	Sweden	199	Sweden	183	Japan	1068
15	Austria	184	Netherlands	172	Czech Republic	1022
16	Argentina	178	Russian Federation	153	Korea, Republic of	1011
17	Hungary	178	Israel	152	Austria	960
18	Brazil	175	Austria	147	Hungary	911
19	Mexico	175	Czech Republic	145	India	897
20	Switzerland	168	Brazil	141	Brazil	864
21	Denmark	167	Hungary	132	Israel	846
22	South Africa	161	China	127	Mexico	820
23	Israel	159	Mexico	116	Denmark	767
24	Japan	145	Romania	112	Argentina	733
25	India	143	Denmark	112	Romania	707
26	Korea, Republic of	139	Taiwan	109	Switzerland	691
27	Finland	133	Switzerland	103	Taiwan	653
28	Romania	113	Argentina	91	South Africa	639
29	Taiwan	110	Finland	84	China	627
30	China	110	Turkey	79	Finland	608

Source: www.clinicaltrials.gov,KoNECT, 2010

Clinical Trials Approved by KFDA

2012년, 총 670건 (33.2%↑), 다국가 303건 (56% ↑), 국내 367건 (18.8%↑)



Source: KFDA 2011

‘12년 식약청 임상시험 승인 현황

•모든 임상시험이 식약청 승인 대상은 아님.
(시판 후 조사 및 대부분의 연구자 주도 임상시험)

•임상시험이 **서울/경기 지역**의 **대형병원**에 집중되어 있음.

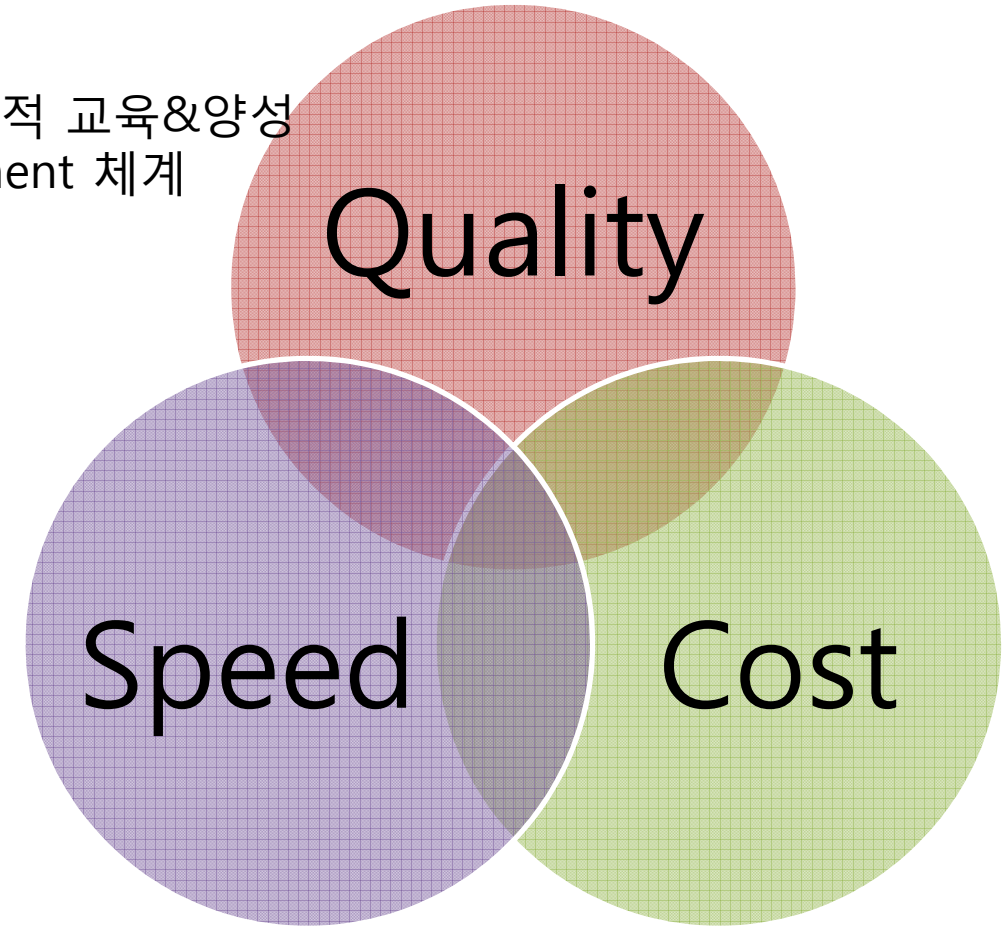
•**지역임상시험센터**를 중심으로 임상시험이 이뤄지고 있음.

순위	임상시험 실시기관	수행 건수
〃	부산대학교병원	64
9위	고려대 의대 안암병원	62
10위	가천의대 중앙길병원	57
〃	인하대 의대 부속병원	57
12위	충남대학교병원	53
13위	고려대 의대 구로병원	48
14위	인제대학교 부산백병원	42
15위	동아대학교병원	41

지역의 한계 극복

기관 및 지역의 지원과 관심 필요

연구자 /CRC 지속적 교육&양성
Quality management 체계



연구자 관심 유도
연구자 간 협력

THANK YOU FOR ATTENTION